(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 January 2002 (10.01.2002)

PCT

(10) International Publication Number
WO 02/02587 A1

(51) International Patent Classification[7]: C07H 21/04, C12N 15/10, 15/11, 15/12

(21) International Application Number: PCT/US01/20917

(22) International Filing Date: 29 June 2001 (29.06.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/215,135 30 June 2000 (30.06.2000) US
60/225,266 14 August 2000 (14.08.2000) US

(71) Applicant *(for all designated States except US)*: **HUMAN GENOME SCIENCES, INC.** [US/US]; 9410 Key West Avenue, Rockville, MD 20850 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **FISCELLA, Michele** [IT/US]; 6308 Redwing Road, Bethesda, MD 20817 (US). **NI, Jian** [CN/US]; 17815 Fair Lady Way, Germantown, MD 20874 (US). **RUBEN, Steven, M.** [US/US]; 18528 Heritage Hills Drive, Olney, MD 20832 (US).

(74) Agents: **HOOVER, Kenley** et al.; 9410 Key West Avenue, Rockville, MD 20850 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*
— *with (an) indication(s) in relation to deposited biological material furnished under Rule 13bis separately from the description*
— *with sequence listing part of description published separately in electronic form and available upon request from the International Bureau*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/02587 A1

(54) Title: B7-LIKE POLYNUCLEOTIDES, POLYPEPTIDES, AND ANTIBODIES

(57) Abstract: The present invention relates to novel human B7-like polypeptides and isolated nucleic acids containing the coding regions of the genes encoding such polypeptides. Also provided are vectors, host cells, antibodies, and recombinant methods for producing human B7-like polypeptides. The invention further relates to diagnostic and therapeutic methods useful for diagnosing and treating disorders related to these novel human B7-like polypeptides.

B7-LIKE POLYNUCLEOTIDES, POLYPEPTIDES, AND ANTIBODIES

FIELD OF THE INVENTION

[1] The present invention relates to novel B7-like proteins. More specifically, isolated nucleic acid molecules are provided encoding novel B7-like polypeptides. Novel B7-like polypeptides and antibodies that bind to these polypeptides are provided. Also provided are vectors, host cells, and recombinant and synthetic methods for producing human B7-like polynucleotides and/or polypeptides. The invention further relates to diagnostic and therapeutic methods useful for diagnosing, treating, preventing and/or prognosing disorders related to these novel B7-like polypeptides. The invention further relates to screening methods for identifying agonists and antagonists of polynucleotides and polypeptides of the invention. The present invention further relates to methods and/or compositions for inhibiting the production and function of the polypeptides of the present invention.

BACKGROUND OF THE INVENTION

[2] Costimulatory interactions between the B7 family ligands and their receptors play critical roles in the growth, differentiation and death of T cells. Engagement of the T cell costimulator CD28 by either specific antibodies or its natural ligands B7-1 and B7-2 increases antigen-specific proliferation of CD4+ T cells, enhances production of cytokines, induces maturation of CD8+ effector T cells, and promotes T cell survival (Chambers, C.A., *et al., Curr. Opin. Immunol., 9*:396-404 (1997); Lenschow, D.J., *et al., Annu. Rev. Immunol., 14*:233-58 (1996); Chen, L., *et al., Immunol. Today, 14*:483-86 (1993); Boise, L.H., *et al., Curr. Opin. Immunol., 7*:620-25 (1995)). Signaling through the homologous CTLA-4 receptor of B7-1 and B7-2 on activated T cells, however, is thought to deliver a negative signal that inhibits T cell proliferation, IL-2 production, and cell cycle progression (Krummel, M.F., *et al., J. Exp. Med., 183*:2533-540 (1996); Walunas, T.L., *et al., J. Exp. Med., 183*:2541-550 (1996)).

[3] Although B7-1 and B7-2 share approximately 20% homology at the amino acid level, the two proteins share similar tertiary structure and costimulatory functions (Peach, R.J.J., *et al., J. Biol. Chem., 270*:21181-187 (1995); Fargeas, C.A., *et al., J. Exp. Med., 182*:667-75 (1995); Bajorath, J., *et al., Protein Sci., 3*:2148-150 (1994); Guo, Y., *et al., Mol. Immunol., 35*:215-25 (1998)).

[4] Recent studies indicate that other members of the B7-CD28 family of proteins may also participate in the regulation of cellular and humoral immune responses. One of the new members is inducible costimulator (ICOS), a CD28-like receptor (Hutloff, A., *et al., Nature, 397*:263-66 (1999)). While the natural ligand for ICOS has not been identified yet, a F44 monoclonal antibody (mAb) against ICOS costimulates T cell growth and increases secretion of several cytokines, including IL-10, IFN-γ, and IL-4, but not IL-2 (Hutloff, A., *et al., Nature, 397*:263-66 (1999)).

[5] Another new B7 family member is mouse B7h, identified by Swallow and colleagues (Swallow, M.M., *et al., Immunity, 11*:423-32 (1999)). B7h does not bind to CD28 and CTLA-4, and can costimulate T cell growth in the presence of antigenic signals. Surface expression of B7h can be up-regulated by TNF-α in 3T3 fibroblast cell lines, and the increase of B7h mRNA is also observed in non-lymphoid tissues exposed to LPS (Swallow, M.M., *et al., Immunity, 11*:423-32 (1999)).

[6] A further recently reported novel member of the human B7 family of proteins is B7-H1 (Dong, H., *et al., Nature Med., 5*:1365-69 (1999)). B7-H1 shares approximately 20% identical amino acid sequence with B7-1 and B7-2 in the Ig V- and Ig C-like extracellular domains, but differs more profoundly from B7-1 and B7-2 in the cytoplasmic domain. Surface expression of B7-H1 can be detected in the majority of activated CD14+ macrophages, and in a fraction of activated T cells. B7-H1 costimulates T cell responses in the presence of the suboptimal doses of anti-CD3 mAb, enhances allogenic mixed lymphocyte responses, and preferentially induces IL-10 secretion from T cells (Dong, H., *et al., Nature Med., 5*:1365-69 (1999)).

[7] Activation of certain cells in the body, such as T cells, can result in the initiation of the inflammatory response, resulting in inflammation. Inflammation, which is characterized by redness, swelling, heat, and pain, is an essential immune response which occurs following tissue injury or infection. The initial event triggers an elaborate signaling cascade which results in increased local blood flow, blood clotting, and vascular permeability. These acute

changes facilitate the recruitment of phagocytic leukocytes to the site of injury or infection. Once at the affected site, the immune cells can begin to neutralize pathogens and contribute to tissue repair.

[8] Among the many protein classes involved in the inflammatory response are blood clotting factors, vasodilating substances (such as histamine and bradykinin), cell adhesion molecules, cytokines (such as interleukins and chemokines), and immune system effector cells (such as neutrophils, macrophages, and lymphocytes).

[9] Although the inflammatory response is an important defense mechanism against infection by foreign substances, inappropriate or excessive activation of inflammation can lead to tissue damage and even death. Medical conditions resulting from inflammation include, but are not limited to, inflammatory bowel disease, multiple sclerosis, arthritis, asthma, allergies, sarcoidosis, septic shock, gastrointestinal cancers, pancreatitis, dermatitis, gout, systemic lupus erythematosis, and Grave's disease. Inflammation is also a potentially life-threatening complication of cardiopulmonary bypass surgery, renal ischemia-reperfusion, and traumatic injury.

[10] Several steroidal and nonsteroidal drugs have been used to control inflammation or to provide symptomatic relief. However, these therapies can be accompanied by numerous side effects which limit their usefulness. Therefore, there is a continuing need for more effective and less toxic alternatives for modulating the inflammatory response.

[11] Thus, there is a further need for polypeptides that are involved in the costimulation of T-cells, since disturbances of such regulation may be involved in disorders relating to the immune system and/or inflammatory disorders. Therefore, there is a need for the identification and characterization of such human polypeptides and antagonists thereof which can play a role in detecting, preventing, ameliorating or correcting such disorders.

SUMMARY OF THE INVENTION

[12] The present invention includes isolated nucleic acid molecules comprising, or alternatively, consisting of a polynucleotide sequence disclosed in the sequence listing and/or contained in a human cDNA plasmid described in Table 1 and deposited with the American Type Culture Collection (ATCC). Fragments, variants, and derivatives of these nucleic acid molecules are also encompassed by the invention. The present invention also includes

isolated nucleic acid molecules comprising, or alternatively, consisting of, a polynucleotide encoding B7-like polypeptides. The present invention further includes B7-like polypeptides encoded by these polynucleotides. Further provided for are amino acid sequences comprising, or alternatively, consisting of, B7-like polypeptides as disclosed in the sequence listing and/or encoded by the human cDNA plasmids described in Table 1 and deposited with the ATCC. Antibodies that bind these polypeptides are also encompassed by the invention. Polypeptide fragments, variants, and derivatives of these amino acid sequences are also encompassed by the invention, as are polynucleotides encoding these polypeptides and antibodies that bind these polypeptides.

DETAILED DESCRIPTION

Tables

[13] Table 1 summarizes ATCC Deposits, Deposit dates, and ATCC designation numbers of deposits made with the ATCC in connection with the present application. Table 1 further summarizes the information pertaining to each "Gene No." described below, including cDNA plasmid identifier, the type of vector contained in the cDNA plasmid identifier, the nucleotide sequence identifier number, nucleotides contained in the disclosed sequence, the location of the 5' nucleotide of the start codon of the disclosed sequence, the amino acid sequence identifier number, and the last amino acid of the ORF encoded by the disclosed sequence.

[14] Table 2 indicates public ESTs, of which at least one, two, three, four, five, ten, or more of any one or more of these public EST sequences are optionally excluded from certain embodiments of the invention.

[15] Table 3 represents the Tabular data for Figure 2, relating to the amino acid analysis of the B7-H8 protein. Alpha, beta, turn and coil regions; hydrophilicity and hydrophobicity; amphipathic regions; flexible regions; antigenic index and surface probability are shown, and all were generated using the default settings of the recited computer algorithyms. Polypeptides comprising, or alternatively consisting of, domains defined by these graphs are contemplated by the present invention, as are polynucleotides encoding these polypeptides.

[16] Table 4 represents the Tabular data for Figure 4, relating to the amino acid analysis of the B7-H7 protein. Alpha, beta, turn and coil regions; hydrophilicity and hydrophobicity;

amphipathic regions; flexible regions; antigenic index and surface probability are shown, and all were generated using the default settings of the recited computer algorithyms. Polypeptides comprising, or alternatively consisting of, domains defined by these graphs are contemplated by the present invention, as are polynucleotides encoding these polypeptides.

[17] Table 5 represents the Tabular data for Figure 6, relating to the amino acid analysis of the B7-H9 protein. Alpha, beta, turn and coil regions; hydrophilicity and hydrophobicity; amphipathic regions; flexible regions; antigenic index and surface probability are shown, and all were generated using the default settings of the recited computer algorithyms. Polypeptides comprising, or alternatively consisting of, domains defined by these graphs are contemplated by the present invention, as are polynucleotides encoding these polypeptides.

[18] Table 6 represents the Tabular data for Figure 8, relating to the amino acid analysis of the B7-H11 protein. Alpha, beta, turn and coil regions; hydrophilicity and hydrophobicity; amphipathic regions; flexible regions; antigenic index and surface probability are shown, and all were generated using the default settings of the recited computer algorithyms. Polypeptides comprising, or alternatively consisting of, domains defined by these graphs are contemplated by the present invention, as are polynucleotides encoding these polypeptides.

[19] Table 7 represents the Tabular data for Figure 10, relating to the amino acid analysis of the B7-H10 protein. Alpha, beta, turn and coil regions; hydrophilicity and hydrophobicity; amphipathic regions; flexible regions; antigenic index and surface probability are shown, and all were generated using the default settings of the recited computer algorithyms. Polypeptides comprising, or alternatively consisting of, domains defined by these graphs are contemplated by the present invention, as are polynucleotides encoding these polypeptides.

[20] Table 8 represents the Tabular data for Figure 12, relating to the amino acid analysis of the B7-H12 protein. Alpha, beta, turn and coil regions; hydrophilicity and hydrophobicity; amphipathic regions; flexible regions; antigenic index and surface probability are shown, and all were generated using the default settings of the recited computer algorithyms. Polypeptides comprising, or alternatively consisting of, domains defined by these graphs are contemplated by the present invention, as are polynucleotides encoding these polypeptides.

[21] Table 9 represents the Tabular data for Figure 14, relating to the amino acid analysis of the B7-H13 protein. Alpha, beta, turn and coil regions; hydrophilicity and

hydrophobicity; amphipathic regions; flexible regions; antigenic index and surface probability are shown, and all were generated using the default settings of the recited computer algorithyms. Polypeptides comprising, or alternatively consisting of, domains defined by these graphs are contemplated by the present invention, as are polynucleotides encoding these polypeptides.

[22] Table 10 summarizes the expression profile of polynucleotides corresponding to the clones disclosed in Table 1. The first column provides a unique clone identifier, "cDNA Plasmid:V", for a cDNA clone related to each contig sequence disclosed in Table 1. Column 2, "Library Code" shows the expression profile of tissue and/or cell line libraries which express the polynucleotides of the invention. Each Library Code in column 2 represents a tissue/cell source identifier code corresponding to the Library Code and Library description provided in Table 12. Expression of these polynucleotides was not observed in the other tissues and/or cell libraries tested. One of skill in the art could routinely use this information to identify tissues which show a predominant expression pattern of the corresponding polynucleotide of the invention or to identify polynucleotides which show predominant and/or specific tissue expression.

[23] Table 11, column 1, provides a nucleotide sequence identifier, "SEQ ID NO:X," that matches a nucleotide SEQ ID NO:X disclosed in Table 1, column 5. Table 11, column 2, provides the chromosomal location, "Cytologic Band or Chromosome," of polynucleotides corresponding to SEQ ID NO:X. Chromosomal location was determined by finding exact matches to EST and cDNA sequences contained in the NCBI (National Center for Biotechnology Information) UniGene database.

[24] Table 12, column 1, provides the Library Code disclosed in Table 10, column 2. Column 2 provides a description of the tissue or cell source from which the corresponding library was derived. Library codes corresponding to diseased tissues are indicated in column 3 with the word "disease". The use of the word "disease" in column 3 is non-limiting. The tissue source of the library may be specific (e.g., a neoplasm), or may be disease-associated (e.g., a tissue sample from a normal portion of a diseased organ). Furthermore, libraries lacking the "disease" designation may still be derived from sources directly or indirectly involved in a disease state or disorder, and therefore may have a further utility in that disease state or disorder.

Figures

[25] Figures 1A-D show the nucleotide (SEQ ID NO: 2) and deduced amino acid sequence (SEQ ID NO: 14) corresponding to the B7-H8 gene.

[26] Figure 2 shows an analysis of the amino acid sequence of the B7-H8 protein (SEQ ID NO: 14). Alpha, beta, turn and coil regions; hydrophilicity and hydrophobicity; amphipathic regions; flexible regions; antigenic index and surface probability are shown, and all were generated using the default settings of the recited computer algorithyms. In the "Antigenic Index or Jameson-Wolf" graph, the positive peaks indicate locations of the highly antigenic regions of the protein, i.e., regions from which epitope-bearing peptides of the invention can be obtained. Polypeptides comprising, or alternatively consisting of, domains defined by these graphs are contemplated by the present invention, as are polynucleotides encoding these polypeptides.

[27] Figures 3A-C show the nucleotide (SEQ ID NO: 3) and deduced amino acid sequence (SEQ ID NO: 15) corresponding to the B7-H7 gene.

[28] Figure 4 shows an analysis of the amino acid sequence of the B7-H7 protein (SEQ ID NO: 15). Alpha, beta, turn and coil regions; hydrophilicity and hydrophobicity; amphipathic regions; flexible regions; antigenic index and surface probability are shown, and all were generated using the default settings of the recited computer algorithyms. In the "Antigenic Index or Jameson-Wolf" graph, the positive peaks indicate locations of the highly antigenic regions of the protein, i.e., regions from which epitope-bearing peptides of the invention can be obtained. Polypeptides comprising, or alternatively consisting of, domains defined by these graphs are contemplated by the present invention, as are polynucleotides encoding these polypeptides.

[29] Figures 5A-C show the nucleotide (SEQ ID NO: 4) and deduced amino acid sequence (SEQ ID NO: 16) corresponding to the B7-H9 gene.

[30] Figure 6 shows an analysis of the amino acid sequence of the B7-H9 protein (SEQ ID NO: 16). Alpha, beta, turn and coil regions; hydrophilicity and hydrophobicity; amphipathic regions; flexible regions; antigenic index and surface probability are shown, and all were generated using the default settings of the recited computer algorithyms. In the "Antigenic Index or Jameson-Wolf" graph, the positive peaks indicate locations of the highly antigenic regions of the protein, i.e., regions from which epitope-bearing peptides of the invention can be obtained. Polypeptides comprising, or alternatively consisting of, domains

defined by these graphs are contemplated by the present invention, as are polynucleotides encoding these polypeptides.

[31] Figures 7A-C show the nucleotide (SEQ ID NO: 5) and deduced amino acid sequence (SEQ ID NO: 17) corresponding to the B7-H11 gene.

[32] Figure 8 shows an analysis of the amino acid sequence of the B7-H11 protein (SEQ ID NO: 17). Alpha, beta, turn and coil regions; hydrophilicity and hydrophobicity; amphipathic regions; flexible regions; antigenic index and surface probability are shown, and all were generated using the default settings of the recited computer algorithyms. In the "Antigenic Index or Jameson-Wolf" graph, the positive peaks indicate locations of the highly antigenic regions of the protein, i.e., regions from which epitope-bearing peptides of the invention can be obtained. Polypeptides comprising, or alternatively consisting of, domains defined by these graphs are contemplated by the present invention, as are polynucleotides encoding these polypeptides.

[33] Figures 9A-B show the nucleotide (SEQ ID NO: 6) and deduced amino acid sequence (SEQ ID NO: 18) corresponding to the B7-H10 gene.

[34] Figure 10 shows an analysis of the amino acid sequence of the B7-H10 protein (SEQ ID NO: 18). Alpha, beta, turn and coil regions; hydrophilicity and hydrophobicity; amphipathic regions; flexible regions; antigenic index and surface probability are shown, and all were generated using the default settings of the recited computer algorithyms. In the "Antigenic Index or Jameson-Wolf" graph, the positive peaks indicate locations of the highly antigenic regions of the protein, i.e., regions from which epitope-bearing peptides of the invention can be obtained. Polypeptides comprising, or alternatively consisting of, domains defined by these graphs are contemplated by the present invention, as are polynucleotides encoding these polypeptides.

[35] Figures 11A-B show the nucleotide (SEQ ID NO: 7) and deduced amino acid sequence (SEQ ID NO: 19) corresponding to the B7-H12 gene.

[36] Figure 12 shows an analysis of the amino acid sequence of the B7-H12 protein (SEQ ID NO: 19). Alpha, beta, turn and coil regions; hydrophilicity and hydrophobicity; amphipathic regions; flexible regions; antigenic index and surface probability are shown, and all were generated using the default settings of the recited computer algorithyms. In the "Antigenic Index or Jameson-Wolf" graph, the positive peaks indicate locations of the highly antigenic regions of the protein, i.e., regions from which epitope-bearing peptides of the

invention can be obtained. Polypeptides comprising, or alternatively consisting of, domains defined by these graphs are contemplated by the present invention, as are polynucleotides encoding these polypeptides.

[37] Figures 13A-C show the nucleotide (SEQ ID NO: 8) and deduced amino acid sequence (SEQ ID NO: 20) corresponding to the B7-H13 gene.

[38] Figure 14 shows an analysis of the amino acid sequence of the B7-H13 protein (SEQ ID NO: 20). Alpha, beta, turn and coil regions; hydrophilicity and hydrophobicity; amphipathic regions; flexible regions; antigenic index and surface probability are shown, and all were generated using the default settings of the recited computer algorithyms. In the "Antigenic Index or Jameson-Wolf" graph, the positive peaks indicate locations of the highly antigenic regions of the protein, i.e., regions from which epitope-bearing peptides of the invention can be obtained. Polypeptides comprising, or alternatively consisting of, domains defined by these graphs are contemplated by the present invention, as are polynucleotides encoding these polypeptides.

Definitions

[39] The following definitions are provided to facilitate understanding of certain terms used throughout this specification.

[40] In the present invention, "isolated" refers to material removed from its original environment (e.g., the natural environment if it is naturally occurring), and thus is altered "by the hand of man" from its natural state. For example, an isolated polynucleotide could be part of a vector or a composition of matter, or could be contained within a cell, and still be "isolated" because that vector, composition of matter, or particular cell is not the original environment of the polynucleotide. The term "isolated" does not refer to genomic or cDNA libraries, whole cell total or mRNA preparations, genomic DNA preparations (including those separated by electrophoresis and transferred onto blots), sheared whole cell genomic DNA preparations or other compositions where the art demonstrates no distinguishing features of the polynucleotide/sequences of the present invention.

[41] As used herein, a "polynucleotide" refers to a molecule having a nucleic acid sequence contained in SEQ ID NO:X (as described in column 5 of Table 1), or cDNA plasmid:V (as described in column 2 of Table 1 and contained within a pool of plasmids deposited with the ATCC in ATCC Deposit No:Z). For example, the polynucleotide can

contain the nucleotide sequence of the full length cDNA sequence, including the 5' and 3' untranslated sequences, the coding region, with or without a natural or artificial signal sequence, the protein coding region, as well as fragments, epitopes, domains, and variants of the nucleic acid sequence. Moreover, as used herein, a "polypeptide" refers to a molecule having an amino acid sequence encoded by a polynucleotide of the invention as broadly defined (obviously excluding poly-Phenylalanine or poly-Lysine peptide sequences which result from translation of a polyA tail of a sequence corresponding to a cDNA).

[42] In the present invention, a representative plasmid containing the sequence of SEQ ID NO:X was deposited with the American Type Culture Collection ("ATCC") and/or described in Table 1. As shown in Table 1, each plasmid is identified by a cDNA Plasmid Identifier and the ATCC Deposit Number (ATCC Deposit No:Z). Plasmids that were pooled and deposited as a single deposit have the same ATCC Deposit Number. The ATCC is located at 10801 University Boulevard, Manassas, Virginia 20110-2209, USA. The ATCC deposit was made pursuant to the terms of the Budapest Treaty on the international recognition of the deposit of microorganisms for purposes of patent procedure.

[43] A "polynucleotide" of the present invention also includes those polynucleotides capable of hybridizing, under stringent hybridization conditions, to sequences contained in SEQ ID NO:X, or the complement thereof (e.g., the complement of any one, two, three, four, or more of the polynucleotide fragments described herein) and/or sequences contained in cDNA plasmid:V (e.g., the complement of any one, two, three, four, or more of the polynucleotide fragments described herein). "Stringent hybridization conditions" refers to an overnight incubation at 42 degree C in a solution comprising 50% formamide, 5x SSC (750 mM NaCl, 75 mM trisodium citrate), 50 mM sodium phosphate (pH 7.6), 5x Denhardt's solution, 10% dextran sulfate, and 20 μg/ml denatured, sheared salmon sperm DNA, followed by washing the filters in 0.1x SSC at about 65 degree C.

[44] Also included within "polynucleotides" of the present invention are nucleic acid molecules that hybridize to the polynucleotides of the present invention at lower stringency hybridization conditions. Changes in the stringency of hybridization and signal detection are primarily accomplished through the manipulation of formamide concentration (lower percentages of formamide result in lowered stringency); salt conditions, or temperature. For example, lower stringency conditions include an overnight incubation at 37 degree C in a solution comprising 6X SSPE (20X SSPE = 3M NaCl; 0.2M NaH_2PO_4; 0.02M EDTA, pH

7.4), 0.5% SDS, 30% formamide, 100 μg/ml salmon sperm blocking DNA; followed by washes at 50 degree C with 1XSSPE, 0.1% SDS. In addition, to achieve even lower stringency, washes performed following stringent hybridization can be done at higher salt concentrations (e.g. 5X SSC).

[45] Note that variations in the above conditions may be accomplished through the inclusion and/or substitution of alternate blocking reagents used to suppress background in hybridization experiments. Typical blocking reagents include Denhardt's reagent, BLOTTO, heparin, denatured salmon sperm DNA, and commercially available proprietary formulations. The inclusion of specific blocking reagents may require modification of the hybridization conditions described above, due to problems with compatibility.

[46] Of course, a polynucleotide which hybridizes only to polyA+ sequences (such as any 3' terminal polyA+ tract of a cDNA shown in the sequence listing), or to a complementary stretch of T (or U) residues, would not be included in the definition of "polynucleotide," since such a polynucleotide would hybridize to any nucleic acid molecule containing a poly (A) stretch or the complement thereof (e.g., practically any double-stranded cDNA clone generated using oligo dT as a primer).

[47] The polynucleotides of the present invention can be composed of any polyribonucleotide or polydeoxribonucleotide, which may be unmodified RNA or DNA or modified RNA or DNA. For example, polynucleotides can be composed of single- and double-stranded DNA, DNA that is a mixture of single- and double-stranded regions, single- and double-stranded RNA, and RNA that is mixture of single- and double-stranded regions, hybrid molecules comprising DNA and RNA that may be single-stranded or, more typically, double-stranded or a mixture of single- and double-stranded regions. In addition, the polynucleotide can be composed of triple-stranded regions comprising RNA or DNA or both RNA and DNA. A polynucleotide may also contain one or more modified bases or DNA or RNA backbones modified for stability or for other reasons. "Modified" bases include, for example, tritylated bases and unusual bases such as inosine. A variety of modifications can be made to DNA and RNA; thus, "polynucleotide" embraces chemically, enzymatically, or metabolically modified forms.

[48] In specific embodiments, the polynucleotides of the invention are at least 15, at least 30, at least 50, at least 100, at least 125, at least 500, or at least 1000 continuous nucleotides but are less than or equal to 300 kb, 200 kb, 100 kb, 50 kb, 15 kb, 10 kb, 7.5kb, 5

kb, 2.5 kb, 2.0 kb, or 1 kb, in length. In a further embodiment, polynucleotides of the invention comprise a portion of the coding sequences, as disclosed herein, but do not comprise all or a portion of any intron. In another embodiment, the polynucleotides comprising coding sequences do not contain coding sequences of a genomic flanking gene (i.e., 5' or 3' to the gene of interest in the genome). In other embodiments, the polynucleotides of the invention do not contain the coding sequence of more than 1000, 500, 250, 100, 50, 25, 20, 15, 10, 5, 4, 3, 2, or 1 genomic flanking gene(s).

[49] "SEQ ID NO:X" refers to a polynucleotide sequence described in column 5 of Table 1, while "SEQ ID NO:Y" refers to a polypeptide sequence described in column 10 of Table 1. SEQ ID NO:X is identified by an integer specified in column 6 of Table 1. The polypeptide sequence SEQ ID NO:Y is a translated open reading frame (ORF) encoded by polynucleotide SEQ ID NO:X. The polynucleotide sequences are shown in the sequence listing immediately followed by all of the polypeptide sequences. Thus, a polypeptide sequence corresponding to polynucleotide sequence SEQ ID NO:2 is the first polypeptide sequence shown in the sequence listing. The second polypeptide sequence corresponds to the polynucleotide sequence shown as SEQ ID NO:3, and so on.

[50] The polypeptides of the present invention can be composed of amino acids joined to each other by peptide bonds or modified peptide bonds, i.e., peptide isosteres, and may contain amino acids other than the 20 gene-encoded amino acids. The polypeptides may be modified by either natural processes, such as posttranslational processing, or by chemical modification techniques which are well known in the art. Such modifications are well described in basic texts and in more detailed monographs, as well as in a voluminous research literature. Modifications can occur anywhere in a polypeptide, including the peptide backbone, the amino acid side-chains and the amino or carboxyl termini. It will be appreciated that the same type of modification may be present in the same or varying degrees at several sites in a given polypeptide. Also, a given polypeptide may contain many types of modifications. Polypeptides may be branched, for example, as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched, and branched cyclic polypeptides may result from posttranslation natural processes or may be made by synthetic methods. Modifications include acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative,

covalent attachment of phosphotidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cysteine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. (See, for instance, PROTEINS - STRUCTURE AND MOLECULAR PROPERTIES, 2nd Ed., T. E. Creighton, W. H. Freeman and Company, New York (1993); POSTTRANSLATIONAL COVALENT MODIFICATION OF PROTEINS, B. C. Johnson, Ed., Academic Press, New York, pgs. 1-12 (1983); Seifter et al., Meth Enzymol 182:626-646 (1990); Rattan et al., Ann NY Acad Sci 663:48-62 (1992)).

[51] The polypeptides of the invention can be prepared in any suitable manner. Such polypeptides include isolated naturally occurring polypeptides, recombinantly produced polypeptides, synthetically produced polypeptides, or polypeptides produced by a combination of these methods. Means for preparing such polypeptides are well understood in the art.

[52] The polypeptides may be in the form of the secreted protein, including the mature form, or may be a part of a larger protein, such as a fusion protein (see below). It is often advantageous to include an additional amino acid sequence which contains secretory or leader sequences, pro-sequences, sequences which aid in purification, such as multiple histidine residues, or an additional sequence for stability during recombinant production.

[53] The polypeptides of the present invention are preferably provided in an isolated form, and preferably are substantially purified. A recombinantly produced version of a polypeptide, including the secreted polypeptide, can be substantially purified using techniques described herein or otherwise known in the art, such as, for example, by the one-step method described in Smith and Johnson, Gene 67:31-40 (1988). Polypeptides of the invention also can be purified from natural, synthetic or recombinant sources using techniques described herein or otherwise known in the art, such as, for example, antibodies of the invention raised against the polypeptides of the present invention in methods which are well known in the art.

[54] By a polypeptide demonstrating a "functional activity" is meant, a polypeptide capable of displaying one or more known functional activities associated with a full-length

(complete) protein of the invention. Such functional activities include, but are not limited to, biological activity, antigenicity [ability to bind (or compete with a polypeptide for binding) to an anti-polypeptide antibody], immunogenicity (ability to generate antibody which binds to a specific polypeptide of the invention), ability to form multimers with polypeptides of the invention, and ability to bind to a receptor for a polypeptide.

[55] "A polypeptide having functional activity" refers to polypeptides exhibiting activity similar, but not necessarily identical to, an activity of a polypeptide of the present invention, including mature forms, as measured in a particular assay, such as, for example, a biological assay, with or without dose dependency. In the case where dose dependency does exist, it need not be identical to that of the polypeptide, but rather substantially similar to the dose-dependence in a given activity as compared to the polypeptide of the present invention (i.e., the candidate polypeptide will exhibit greater activity or not more than about 25-fold less and, preferably, not more than about tenfold less activity, and most preferably, not more than about three-fold less activity relative to the polypeptide of the present invention).

[56] The functional activity of the polypeptides, and fragments, variants derivatives, and analogs thereof, can be assayed by various methods.

[57] For example, in one embodiment where one is assaying for the ability to bind or compete with full-length polypeptide of the present invention for binding to an antibody to the full length polypeptide, various immunoassays known in the art can be used, including but not limited to, competitive and non-competitive assay systems using techniques such as radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoradiometric assays, gel diffusion precipitation reactions, immunodiffusion assays, in situ immunoassays (using colloidal gold, enzyme or radioisotope labels, for example), western blots, precipitation reactions, agglutination assays (e.g., gel agglutination assays, hemagglutination assays), complement fixation assays, immunofluorescence assays, protein A assays, and immunoelectrophoresis assays, etc. In one embodiment, antibody binding is detected by detecting a label on the primary antibody. In another embodiment, the primary antibody is detected by detecting binding of a secondary antibody or reagent to the primary antibody. In a further embodiment, the secondary antibody is labeled. Many means are known in the art for detecting binding in an immunoassay and are within the scope of the present invention.

[58] In another embodiment, where a ligand is identified, or the ability of a polypeptide fragment, variant or derivative of the invention to multimerize is being evaluated, binding can be assayed, e.g., by means well-known in the art, such as, for example, reducing and non-reducing gel chromatography, protein affinity chromatography, and affinity blotting. See generally, Phizicky, E., et al., Microbiol. Rev. 59:94-123 (1995). In another embodiment, physiological correlates polypeptide of the present invention binding to its substrates (signal transduction) can be assayed.

[59] In addition, assays described herein (see Examples) and otherwise known in the art may routinely be applied to measure the ability of polypeptides of the present invention and fragments, variants derivatives and analogs thereof to elicit polypeptide related biological activity (either in vitro or in vivo). Other methods will be known to the skilled artisan and are within the scope of the invention.

FEATURES OF PROTEIN ENCODED BY GENE NO: 1

[60] For purposes of this application, this gene and its corresponding translation product are known as the B7-H8 gene and B7-H8 protein. This protein is believed to reside as a cell-surface molecule, and the transmembrane domain of this protein is believed to approximately embody the following preferred amino acid residues: SKASLCVSSFFAISWALLPL (SEQ ID NO: 26). Polynucleotides encoding these polypeptides are also encompassed by the invention, as are antibodies that bind one or more of these peptides. As one skilled in the art would understand, the transmembrane domain was predicted using computer analysis, and the transmembrane domain may vary by one, two, three, four, five, six, seven, eight, nine, and/or ten amino acids from the N and C-termini of the predicted transmembrane domain. The B7-H8 gene shares sequence homology with members of the B7 family of ligands (i.e., B7-1 (See Genbank Accession AAF25807)). These proteins and their corresponding receptors play vital roles in the growth, differentiation, activation, proliferation and death of T cells. For example, some members of this family (i.e., B7-H1) are involved in costimulation of the T cell response, as well as inducing increased cytokine production, while other family members are involved in the negative regulation of the T cell response. Therefore, agonists and antagonists, such as antibodies or small molecules directed against translation products of the B7-H8 gene are useful for treating T cell mediated immune system

disorders, as well as disorders of other immune system cells, such as for example, neutrophils, macrophage, and leukocytes.

[61] Preferred polypeptides of the present invention comprise, or alternatively consist of, one or both of the immunogenic epitopes shown in SEQ ID NO: 14 as residues: Lys-84 to Glu-95 and Ser-243 to Ser-249. Polynucleotides encoding these polypeptides are also encompassed by the invention, as are antibodies that bind one or more of these polypeptides. Moreover, fragments and variants of these polypeptides (e.g., fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof) are encompassed by the invention. Antibodies that bind these fragments and variants of the invention are also encompassed by the invention. Polynucleotides encoding these fragments and variants are also encompassed by the invention.

[62] In nonexclusive embodiments, polypeptides of the invention comprise, or alternatively consist of, an amino acid sequence selected from the group consisting of:

[63] The extracellular domain of the B7-H8 protein: MASLGQILFWSIISIIIILAGAIALIIGFGISGRHSITVTTVASAGNIGEDGILSCTFEPDIKL SDIVIQWLKEGVLGLVHEFKEGKDELSEQDEMFRGRTAVFADQVIVGNASLRLKNV QLTDAGTYKCYIITSKGKGNANLEYKTGAFSMPEVNVDYNASSETLRCEAPRWFPQP TVVWASQVDQGANFSEVSNTSFELNSENVTMKVVSVLYNVTINNTYSCMIENDIAK ATGDIKVTESEIKRRSHLQLLN (SEQ ID NO: 27),

[64] The mature extracellular domain of the B7-H8 protein: LIIGFGISGRHSITVTTVASAGNIGEDGILSCTFEPDIKLSDIVIQWLKEGVLGLVHEFKE GKDELSEQDEMFRGRTAVFADQVIVGNASLRLKNVQLTDAGTYKCYIITSKGKGNA NLEYKTGAFSMPEVNVDYNASSETLRCEAPRWFPQPTVVWASQVDQGANFSEVSNT SFELNSENVTMKVVSVLYNVTINNTYSCMIENDIAKATGDIKVTESEIKRRSHLQLLN (SEQ ID NO: 28), and/or

[65] The leader sequence of the B7-H8 protein: MASLGQILFWSIISIIIILAGAIA (SEQ ID NO: 29). Polynucleotides encoding these polypeptides are also encompassed by the invention, as are antibodies that bind one or more of these polypeptides. Moreover, fragments and variants of these polypeptides (e.g., fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and

polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof) are encompassed by the invention. Antibodies that bind these fragments and variants of the invention are also encompassed by the invention. Polynucleotides encoding these fragments and variants are also encompassed by the invention.

[66] Also preferred are polypeptides comprising, or alternatively consisting of, fragments of the mature extracellular portion of the B7-H8 protein demonstrating functional activity (SEQ ID NO: 28). Fragments and/or variants of these polypeptides, such as, for example, fragments and/or variants as described herein, are encompassed by the invention. Polynucleotides encoding these polypeptides (including fragments and/or variants) are also encompassed by the invention, as are antibodies that bind these polypeptides.

[67] By functional activity is meant, a polypeptide fragment capable of displaying one or more known functional activities associated with the full-length (complete) B7-H8 protein. Such functional activities include, but are not limited to, biological activity (e.g., T cell costimulatory activity, ability to bind ICOS, CD28 or CTLA4, and ability to induce or inhibit cytokine production), antigenicity [ability to bind (or compete with a B7-H8 polypeptide for binding) to an anti-B7-H8 antibody], immunogenicity (ability to generate antibody which binds to a B7-H8 polypeptide), ability to form multimers with B7-H8 polypeptides of the invention, and ability to bind to a receptor for a B7-H8 polypeptide.

[68] Figures 1A-D show the nucleotide (SEQ ID NO: 2) and deduced amino acid sequence (SEQ ID NO: 14) corresponding to this gene. Figure 2 shows an analysis of the amino acid sequence (SEQ ID NO: 14). Alpha, beta, turn and coil regions; hydrophilicity and hydrophobicity; amphipathic regions; flexible regions; antigenic index and surface probability are shown, and all were generated using the default settings of the recited computer algorithyms. In the "Antigenic Index or Jameson-Wolf" graph, the positive peaks indicate locations of the highly antigenic regions of the protein, i.e., regions from which epitope-bearing peptides of the invention can be obtained. Polypeptides comprising, or alternatively consisting of, domains defined by these graphs are contemplated by the present invention, as are polynucleotides encoding these polypeptides. The data presented in Figure 2 are also represented in tabular form in Table 3. The columns are labeled with the headings "Res", "Position", and Roman Numerals I-XIV. The column headings refer to the following features of the amino acid sequence presented in Figure 2, and Table 3: "Res": amino acid

residue of SEQ ID NO: 14 and Figures 1A-D; "Position": position of the corresponding residue within SEQ ID NO: 14 and Figures 1A-D; I: Alpha, Regions - Garnier-Robson; II: Alpha, Regions - Chou-Fasman; III: Beta, Regions - Garnier-Robson; IV: Beta, Regions - Chou-Fasman; V: Turn, Regions - Garnier-Robson; VI: Turn, Regions - Chou-Fasman; VII: Coil, Regions - Garnier-Robson; VIII: Hydrophilicity Plot - Kyte-Doolittle; IX: Hydrophobicity Plot - Hopp-Woods; X: Alpha, Amphipathic Regions - Eisenberg; XI: Beta, Amphipathic Regions - Eisenberg; XII: Flexible Regions - Karplus-Schulz; XIII: Antigenic Index - Jameson-Wolf; and XIV: Surface Probability Plot - Emini. Preferred embodiments of the invention in this regard include fragments that comprise, or alternatively consisting of, one or more of the following regions: alpha-helix and alpha-helix forming regions ("alpha-regions"), beta-sheet and beta-sheet forming regions ("beta-regions"), turn and turn-forming regions ("turn-regions"), coil and coil-forming regions ("coil-regions"), hydrophilic regions, hydrophobic regions, alpha amphipathic regions, beta amphipathic regions, flexible regions, surface-forming regions and high antigenic index regions. The data representing the structural or functional attributes of the protein set forth in Figure 2 and/or Table 3, as described above, was generated using the various modules and algorithms of the DNA*STAR set on default parameters. In a preferred embodiment, the data presented in columns VIII, IX, XIII, and XIV of Table 3 can be used to determine regions of the protein which exhibit a high degree of potential for antigenicity. Regions of high antigenicity are determined from the data presented in columns VIII, IX, XIII, and/or XIV by choosing values which represent regions of the polypeptide which are likely to be exposed on the surface of the polypeptide in an environment in which antigen recognition may occur in the process of initiation of an immune response. Certain preferred regions in these regards are set out in Figure 2, but may, as shown in Table 3, be represented or identified by using tabular representations of the data presented in Figure 2. The DNA*STAR computer algorithm used to generate Figure 2 (set on the original default parameters) was used to present the data in Figure 2 in a tabular format (See Table 3). The tabular format of the data in Figure 2 (See Table 3) is used to easily determine specific boundaries of a preferred region.

[69] The present invention is further directed to fragments of the polynucleotide sequences described herein. By a fragment of, for example, the polynucleotide sequence of a deposited cDNA or the nucleotide sequence shown in SEQ ID NO: 2, is intended polynucleotide fragments at least about 15nt, and more preferably at least about 20 nt, at least

about 25nt, still more preferably at least about 30 nt, at least about 35nt, and even more preferably, at least about 40 nt in length, at least about 45nt in length, at least about 50nt in length, at least about 60nt in length, at least about 70nt in length, at least about 80nt in length, at least about 90nt in length, at least about 100nt in length, at least about 125nt in length, at least about 150nt in length, at least about 175nt in length, which are useful as diagnostic probes and primers as discussed herein. Of course, larger fragments 200-1500 nt in length are also useful according to the present invention, as are fragments corresponding to most, if not all, of the nucleotide sequence of a deposited cDNA or as shown in SEQ ID NO: 2. By a fragment at least 20 nt in length, for example, is intended fragments which include 20 or more contiguous bases from the nucleotide sequence of a deposited cDNA or the nucleotide sequence as shown in SEQ ID NO: 2. In this context "about" includes the particularly recited size, an sizes larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Representative examples of polynucleotide fragments of the invention include, for example, fragments that comprise, or alternatively, consist of, a sequence from about nucleotide 1 to about 50, from about 51 to about 100, from about 101 to about 150, from about 151 to about 200, from about 201 to about 250, from about 251 to about 300, from about 301 to about 350, from about 351 to about 400, from about 401 to about 450, from about 451 to about 500, and from about 501 to about 550, and from about 551 to about 600, from about 601 to about 650, from about 651 to about 700, from about 701 to about 750, from about 751 to about 800, and from about 801 to about 860, of SEQ ID NO: 2, or the complementary strand thereto, or the cDNA contained in a deposited clone. In this context "about" includes the particularly recited ranges, and ranges larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. In additional embodiments, the polynucleotides of the invention encode functional attributes of the corresponding protein.

[70] Preferred polypeptide fragments of the invention comprise, or alternatively consist of, the secreted protein having a continuous series of deleted residues from the amino or the carboxy terminus, or both. Particularly, N-terminal deletions of the polypeptide can be described by the general formula m-282 where m is an integer from 2 to 277, where m corresponds to the position of the amino acid residue identified in SEQ ID NO: 14. More in particular, the invention provides polynucleotides encoding polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group: A-2 to K-282; S-3 to K-282; L-4 to K-282; G-5 to K-282; Q-6 to K-282; I-7 to K-282; L-8 to K-282; F-9 to K-

282; W-10 to K-282; S-11 to K-282; I-12 to K-282; I-13 to K-282; S-14 to K-282; I-15 to K-282; I-16 to K-282; I-17 to K-282; I-18 to K-282; L-19 to K-282; A-20 to K-282; G-21 to K-282; A-22 to K-282; I-23 to K-282; A-24 to K-282; L-25 to K-282; I-26 to K-282; I-27 to K-282; G-28 to K-282; F-29 to K-282; G-30 to K-282; I-31 to K-282; S-32 to K-282; G-33 to K-282; R-34 to K-282; H-35 to K-282; S-36 to K-282; I-37 to K-282; T-38 to K-282; V-39 to K-282; T-40 to K-282; T-41 to K-282; V-42 to K-282; A-43 to K-282; S-44 to K-282; A-45 to K-282; G-46 to K-282; N-47 to K-282; I-48 to K-282; G-49 to K-282; E-50 to K-282; D-51 to K-282; G-52 to K-282; I-53 to K-282; L-54 to K-282; S-55 to K-282; C-56 to K-282; T-57 to K-282; F-58 to K-282; E-59 to K-282; P-60 to K-282; D-61 to K-282; I-62 to K-282; K-63 to K-282; L-64 to K-282; S-65 to K-282; D-66 to K-282; I-67 to K-282; V-68 to K-282; I-69 to K-282; Q-70 to K-282; W-71 to K-282; L-72 to K-282; K-73 to K-282; E-74 to K-282; G-75 to K-282; V-76 to K-282; L-77 to K-282; G-78 to K-282; L-79 to K-282; V-80 to K-282; H-81 to K-282; E-82 to K-282; F-83 to K-282; K-84 to K-282; E-85 to K-282; G-86 to K-282; K-87 to K-282; D-88 to K-282; E-89 to K-282; L-90 to K-282; S-91 to K-282; E-92 to K-282; Q-93 to K-282; D-94 to K-282; E-95 to K-282; M-96 to K-282; F-97 to K-282; R-98 to K-282; G-99 to K-282; R-100 to K-282; T-101 to K-282; A-102 to K-282; V-103 to K-282; F-104 to K-282; A-105 to K-282; D-106 to K-282; Q-107 to K-282; V-108 to K-282; I-109 to K-282; V-110 to K-282; G-111 to K-282; N-112 to K-282; A-113 to K-282; S-114 to K-282; L-115 to K-282; R-116 to K-282; L-117 to K-282; K-118 to K-282; N-119 to K-282; V-120 to K-282; Q-121 to K-282; L-122 to K-282; T-123 to K-282; D-124 to K-282; A-125 to K-282; G-126 to K-282; T-127 to K-282; Y-128 to K-282; K-129 to K-282; C-130 to K-282; Y-131 to K-282; I-132 to K-282; I-133 to K-282; T-134 to K-282; S-135 to K-282; K-136 to K-282; G-137 to K-282; K-138 to K-282; G-139 to K-282; N-140 to K-282; A-141 to K-282; N-142 to K-282; L-143 to K-282; E-144 to K-282; Y-145 to K-282; K-146 to K-282; T-147 to K-282; G-148 to K-282; A-149 to K-282; F-150 to K-282; S-151 to K-282; M-152 to K-282; P-153 to K-282; E-154 to K-282; V-155 to K-282; N-156 to K-282; V-157 to K-282; D-158 to K-282; Y-159 to K-282; N-160 to K-282; A-161 to K-282; S-162 to K-282; S-163 to K-282; E-164 to K-282; T-165 to K-282; L-166 to K-282; R-167 to K-282; C-168 to K-282; E-169 to K-282; A-170 to K-282; P-171 to K-282; R-172 to K-282; W-173 to K-282; F-174 to K-282; P-175 to K-282; Q-176 to K-282; P-177 to K-282; T-178 to K-282; V-179 to K-282; V-180 to K-282; W-181 to K-282; A-182 to K-282; S-183 to K-282; Q-184 to K-282; V-185 to K-282; D-186 to K-282; Q-187 to K-282; G-188 to K-282; A-189 to K-282; N-190

to K-282; F-191 to K-282; S-192 to K-282; E-193 to K-282; V-194 to K-282; S-195 to K-282; N-196 to K-282; T-197 to K-282; S-198 to K-282; F-199 to K-282; E-200 to K-282; L-201 to K-282; N-202 to K-282; S-203 to K-282; E-204 to K-282; N-205 to K-282; V-206 to K-282; T-207 to K-282; M-208 to K-282; K-209 to K-282; V-210 to K-282; V-211 to K-282; S-212 to K-282; V-213 to K-282; L-214 to K-282; Y-215 to K-282; N-216 to K-282; V-217 to K-282; T-218 to K-282; I-219 to K-282; N-220 to K-282; N-221 to K-282; T-222 to K-282; Y-223 to K-282; S-224 to K-282; C-225 to K-282; M-226 to K-282; I-227 to K-282; E-228 to K-282; N-229 to K-282; D-230 to K-282; I-231 to K-282; A-232 to K-282; K-233 to K-282; A-234 to K-282; T-235 to K-282; G-236 to K-282; D-237 to K-282; I-238 to K-282; K-239 to K-282; V-240 to K-282; T-241 to K-282; E-242 to K-282; S-243 to K-282; E-244 to K-282; I-245 to K-282; K-246 to K-282; R-247 to K-282; R-248 to K-282; S-249 to K-282; H-250 to K-282; L-251 to K-282; Q-252 to K-282; L-253 to K-282; L-254 to K-282; N-255 to K-282; S-256 to K-282; K-257 to K-282; A-258 to K-282; S-259 to K-282; L-260 to K-282; C-261 to K-282; V-262 to K-282; S-263 to K-282; S-264 to K-282; F-265 to K-282; F-266 to K-282; A-267 to K-282; I-268 to K-282; S-269 to K-282; W-270 to K-282; A-271 to K-282; L-272 to K-282; L-273 to K-282; P-274 to K-282; L-275 to K-282; S-276 to K-282; and/or P-277 to K-282 of SEQ ID NO: 14. Polynucleotides encoding these polypeptides are also encompassed by the invention, as are antibodies that bind one or more of these polypeptides. Moreover, fragments and variants of these polypeptides (e.g., fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof) are encompassed by the invention. Antibodies that bind these fragments and variants of the invention are also encompassed by the invention. Polynucleotides encoding these fragments and variants are also encompassed by the invention.

[71] Accordingly, the present invention further provides polypeptides having one or more residues deleted from the carboxy terminus of the amino acid sequence of the polypeptide shown in Figures 1A-D (SEQ ID NO: 14), as described by the general formula 1-n, where n is an integer from 7 to 281, where n corresponds to the position of the amino acid residue identified in SEQ ID NO: 14. Additionally, the invention provides polynucleotides encoding polypeptides comprising, or alternatively consisting of, an amino acid sequence

selected from the following group of C-terminal deletions: M-1 to L-281; M-1 to M-280; M-1 to L-279; M-1 to Y-278; M-1 to P-277; M-1 to S-276; M-1 to L-275; M-1 to P-274; M-1 to L-273; M-1 to L-272; M-1 to A-271; M-1 to W-270; M-1 to S-269; M-1 to I-268; M-1 to A-267; M-1 to F-266; M-1 to F-265; M-1 to S-264; M-1 to S-263; M-1 to V-262; M-1 to C-261; M-1 to L-260; M-1 to S-259; M-1 to A-258; M-1 to K-257; M-1 to S-256; M-1 to N-255; M-1 to L-254; M-1 to L-253; M-1 to Q-252; M-1 to L-251; M-1 to H-250; M-1 to S-249; M-1 to R-248; M-1 to R-247; M-1 to K-246; M-1 to I-245; M-1 to E-244; M-1 to S-243; M-1 to E-242; M-1 to T-241; M-1 to V-240; M-1 to K-239; M-1 to I-238; M-1 to D-237; M-1 to G-236; M-1 to T-235; M-1 to A-234; M-1 to K-233; M-1 to A-232; M-1 to I-231; M-1 to D-230; M-1 to N-229; M-1 to E-228; M-1 to I-227; M-1 to M-226; M-1 to C-225; M-1 to S-224; M-1 to Y-223; M-1 to T-222; M-1 to N-221; M-1 to N-220; M-1 to I-219; M-1 to T-218; M-1 to V-217; M-1 to N-216; M-1 to Y-215; M-1 to L-214; M-1 to V-213; M-1 to S-212; M-1 to V-211; M-1 to V-210; M-1 to K-209; M-1 to M-208; M-1 to T-207; M-1 to V-206; M-1 to N-205; M-1 to E-204; M-1 to S-203; M-1 to N-202; M-1 to L-201; M-1 to E-200; M-1 to F-199; M-1 to S-198; M-1 to T-197; M-1 to N-196; M-1 to S-195; M-1 to V-194; M-1 to E-193; M-1 to S-192; M-1 to F-191; M-1 to N-190; M-1 to A-189; M-1 to G-188; M-1 to Q-187; M-1 to D-186; M-1 to V-185; M-1 to Q-184; M-1 to S-183; M-1 to A-182; M-1 to W-181; M-1 to V-180; M-1 to V-179; M-1 to T-178; M-1 to P-177; M-1 to Q-176; M-1 to P-175; M-1 to F-174; M-1 to W-173; M-1 to R-172; M-1 to P-171; M-1 to A-170; M-1 to E-169; M-1 to C-168; M-1 to R-167; M-1 to L-166; M-1 to T-165; M-1 to E-164; M-1 to S-163; M-1 to S-162; M-1 to A-161; M-1 to N-160; M-1 to Y-159; M-1 to D-158; M-1 to V-157; M-1 to N-156; M-1 to V-155; M-1 to E-154; M-1 to P-153; M-1 to M-152; M-1 to S-151; M-1 to F-150; M-1 to A-149; M-1 to G-148; M-1 to T-147; M-1 to K-146; M-1 to Y-145; M-1 to E-144; M-1 to L-143; M-1 to N-142; M-1 to A-141; M-1 to N-140; M-1 to G-139; M-1 to K-138; M-1 to G-137; M-1 to K-136; M-1 to S-135; M-1 to T-134; M-1 to I-133; M-1 to I-132; M-1 to Y-131; M-1 to C-130; M-1 to K-129; M-1 to Y-128; M-1 to T-127; M-1 to G-126; M-1 to A-125; M-1 to D-124; M-1 to T-123; M-1 to L-122; M-1 to Q-121; M-1 to V-120; M-1 to N-119; M-1 to K-118; M-1 to L-117; M-1 to R-116; M-1 to L-115; M-1 to S-114; M-1 to A-113; M-1 to N-112; M-1 to G-111; M-1 to V-110; M-1 to I-109; M-1 to V-108; M-1 to Q-107; M-1 to D-106; M-1 to A-105; M-1 to F-104; M-1 to V-103; M-1 to A-102; M-1 to T-101; M-1 to R-100; M-1 to G-99; M-1 to R-98; M-1 to F-97; M-1 to M-96; M-1 to E-95; M-1 to D-94; M-1 to Q-93; M-1 to E-92; M-1 to S-91; M-1 to L-

90; M-1 to E-89; M-1 to D-88; M-1 to K-87; M-1 to G-86; M-1 to E-85; M-1 to K-84; M-1 to F-83; M-1 to E-82; M-1 to H-81; M-1 to V-80; M-1 to L-79; M-1 to G-78; M-1 to L-77; M-1 to V-76; M-1 to G-75; M-1 to E-74; M-1 to K-73; M-1 to L-72; M-1 to W-71; M-1 to Q-70; M-1 to I-69; M-1 to V-68; M-1 to I-67; M-1 to D-66; M-1 to S-65; M-1 to L-64; M-1 to K-63; M-1 to I-62; M-1 to D-61; M-1 to P-60; M-1 to E-59; M-1 to F-58; M-1 to T-57; M-1 to C-56; M-1 to S-55; M-1 to L-54; M-1 to I-53; M-1 to G-52; M-1 to D-51; M-1 to E-50; M-1 to G-49; M-1 to I-48; M-1 to N-47; M-1 to G-46; M-1 to A-45; M-1 to S-44; M-1 to A-43; M-1 to V-42; M-1 to T-41; M-1 to T-40; M-1 to V-39; M-1 to T-38; M-1 to I-37; M-1 to S-36; M-1 to H-35; M-1 to R-34; M-1 to G-33; M-1 to S-32; M-1 to I-31; M-1 to G-30; M-1 to F-29; M-1 to G-28; M-1 to I-27; M-1 to I-26; M-1 to L-25; M-1 to A-24; M-1 to I-23; M-1 to A-22; M-1 to G-21; M-1 to A-20; M-1 to L-19; M-1 to I-18; M-1 to I-17; M-1 to I-16; M-1 to I-15; M-1 to S-14; M-1 to I-13; M-1 to I-12; M-1 to S-11; M-1 to W-10; M-1 to F-9; M-1 to L-8; and/or M-1 to I-7 of SEQ ID NO: 14. Polynucleotides encoding these polypeptides are also encompassed by the invention, as are antibodies that bind one or more of these polypeptides. Moreover, fragments and variants of these polypeptides (e.g., fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof) are encompassed by the invention. Antibodies that bind these fragments and variants of the invention are also encompassed by the invention. Polynucleotides encoding these fragments and variants are also encompassed by the invention.

[72] Also as mentioned above, even if deletion of one or more amino acids from the C-terminus of a protein results in modification of loss of one or more biological functions of the protein (e.g., ability to inhibit the Mixed Lymphocyte Reaction), other functional activities (e.g., biological activities, ability to multimerize, ability to bind receptor, ability to induce antibodies, ability to bind antibodies) may still be retained. For example, the ability of the shortened polypeptide to induce and/or bind to antibodies which recognize the complete or mature forms of the polypeptide generally will be retained when less than the majority of the residues of the complete or mature polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and

otherwise known in the art. It is not unlikely that a polypeptide with a large number of deleted C-terminal amino acid residues may retain some biological or immunogenic activities. In fact, peptides composed of as few as six amino acid residues may often evoke an immune response.

[73] More in particular, the invention provides polynucleotides encoding polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group of N-terminal deletions of the mature extracellular portion of the B7-H8 protein (SEQ ID NO: 28): I-26 to N-255; I-27 to N-255; G-28 to N-255; F-29 to N-255; G-30 to N-255; I-31 to N-255; S-32 to N-255; G-33 to N-255; R-34 to N-255; H-35 to N-255; S-36 to N-255; I-37 to N-255; T-38 to N-255; V-39 to N-255; T-40 to N-255; T-41 to N-255; V-42 to N-255; A-43 to N-255; S-44 to N-255; A-45 to N-255; G-46 to N-255; N-47 to N-255; I-48 to N-255; G-49 to N-255; E-50 to N-255; D-51 to N-255; G-52 to N-255; I-53 to N-255; L-54 to N-255; S-55 to N-255; C-56 to N-255; T-57 to N-255; F-58 to N-255; E-59 to N-255; P-60 to N-255; D-61 to N-255; I-62 to N-255; K-63 to N-255; L-64 to N-255; S-65 to N-255; D-66 to N-255; I-67 to N-255; V-68 to N-255; I-69 to N-255; Q-70 to N-255; W-71 to N-255; L-72 to N-255; K-73 to N-255; E-74 to N-255; G-75 to N-255; V-76 to N-255; L-77 to N-255; G-78 to N-255; L-79 to N-255; V-80 to N-255; H-81 to N-255; E-82 to N-255; F-83 to N-255; K-84 to N-255; E-85 to N-255; G-86 to N-255; K-87 to N-255; D-88 to N-255; E-89 to N-255; L-90 to N-255; S-91 to N-255; E-92 to N-255; Q-93 to N-255; D-94 to N-255; E-95 to N-255; M-96 to N-255; F-97 to N-255; R-98 to N-255; G-99 to N-255; R-100 to N-255; T-101 to N-255; A-102 to N-255; V-103 to N-255; F-104 to N-255; A-105 to N-255; D-106 to N-255; Q-107 to N-255; V-108 to N-255; I-109 to N-255; V-110 to N-255; G-111 to N-255; N-112 to N-255; A-113 to N-255; S-114 to N-255; L-115 to N-255; R-116 to N-255; L-117 to N-255; K-118 to N-255; N-119 to N-255; V-120 to N-255; Q-121 to N-255; L-122 to N-255; T-123 to N-255; D-124 to N-255; A-125 to N-255; G-126 to N-255; T-127 to N-255; Y-128 to N-255; K-129 to N-255; C-130 to N-255; Y-131 to N-255; I-132 to N-255; I-133 to N-255; T-134 to N-255; S-135 to N-255; K-136 to N-255; G-137 to N-255; K-138 to N-255; G-139 to N-255; N-140 to N-255; A-141 to N-255; N-142 to N-255; L-143 to N-255; E-144 to N-255; Y-145 to N-255; K-146 to N-255; T-147 to N-255; G-148 to N-255; A-149 to N-255; F-150 to N-255; S-151 to N-255; M-152 to N-255; P-153 to N-255; E-154 to N-255; V-155 to N-255; N-156 to N-255; V-157 to N-255; D-158 to N-255; Y-159 to N-255; N-160 to N-255; A-161 to N-255; S-162 to N-255; S-163 to N-255; E-164 to N-255; T-165 to N-255; L-166 to

N-255; R-167 to N-255; C-168 to N-255; E-169 to N-255; A-170 to N-255; P-171 to N-255; R-172 to N-255; W-173 to N-255; F-174 to N-255; P-175 to N-255; Q-176 to N-255; P-177 to N-255; T-178 to N-255; V-179 to N-255; V-180 to N-255; W-181 to N-255; A-182 to N-255; S-183 to N-255; Q-184 to N-255; V-185 to N-255; D-186 to N-255; Q-187 to N-255; G-188 to N-255; A-189 to N-255; N-190 to N-255; F-191 to N-255; S-192 to N-255; E-193 to N-255; V-194 to N-255; S-195 to N-255; N-196 to N-255; T-197 to N-255; S-198 to N-255; F-199 to N-255; E-200 to N-255; L-201 to N-255; N-202 to N-255; S-203 to N-255; E-204 to N-255; N-205 to N-255; V-206 to N-255; T-207 to N-255; M-208 to N-255; K-209 to N-255; V-210 to N-255; V-211 to N-255; S-212 to N-255; V-213 to N-255; L-214 to N-255; Y-215 to N-255; N-216 to N-255; V-217 to N-255; T-218 to N-255; I-219 to N-255; N-220 to N-255; N-221 to N-255; T-222 to N-255; Y-223 to N-255; S-224 to N-255; C-225 to N-255; M-226 to N-255; I-227 to N-255; E-228 to N-255; N-229 to N-255; D-230 to N-255; I-231 to N-255; A-232 to N-255; K-233 to N-255; A-234 to N-255; T-235 to N-255; G-236 to N-255; D-237 to N-255; I-238 to N-255; K-239 to N-255; V-240 to N-255; T-241 to N-255; E-242 to N-255; S-243 to N-255; E-244 to N-255; I-245 to N-255; K-246 to N-255; R-247 to N-255; R-248 to N-255; S-249 to N-255; and/or H-250 to N-255 of SEQ ID NO: 14. Polynucleotides encoding these polypeptides are also encompassed by the invention, as are antibodies that bind one or more of these polypeptides. Moreover, fragments and variants of these polypeptides (e.g., fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof) are encompassed by the invention. Antibodies that bind these fragments and variants of the invention are also encompassed by the invention. Polynucleotides encoding these fragments and variants are also encompassed by the invention.

[74] Additionally, the invention provides polynucleotides encoding polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group of C-terminal deletions of the mature extracellular portion of the B7-H8 protein (SEQ ID NO: 28): L-25 to L-254; L-25 to L-253; L-25 to Q-252; L-25 to L-251; L-25 to H-250; L-25 to S-249; L-25 to R-248; L-25 to R-247; L-25 to K-246; L-25 to I-245; L-25 to E-244; L-25 to S-243; L-25 to E-242; L-25 to T-241; L-25 to V-240; L-25 to K-239; L-25 to I-238; L-25 to D-237; L-25 to G-236; L-25 to T-235; L-25 to A-234; L-25 to K-233; L-25 to A-232; L-25 to I-

231; L-25 to D-230; L-25 to N-229; L-25 to E-228; L-25 to I-227; L-25 to M-226; L-25 to C-225; L-25 to S-224; L-25 to Y-223; L-25 to T-222; L-25 to N-221; L-25 to N-220; L-25 to I-219; L-25 to T-218; L-25 to V-217; L-25 to N-216; L-25 to Y-215; L-25 to L-214; L-25 to V-213; L-25 to S-212; L-25 to V-211; L-25 to V-210; L-25 to K-209; L-25 to M-208; L-25 to T-207; L-25 to V-206; L-25 to N-205; L-25 to E-204; L-25 to S-203; L-25 to N-202; L-25 to L-201; L-25 to E-200; L-25 to F-199; L-25 to S-198; L-25 to T-197; L-25 to N-196; L-25 to S-195; L-25 to V-194; L-25 to E-193; L-25 to S-192; L-25 to F-191; L-25 to N-190; L-25 to A-189; L-25 to G-188; L-25 to Q-187; L-25 to D-186; L-25 to V-185; L-25 to Q-184; L-25 to S-183; L-25 to A-182; L-25 to W-181; L-25 to V-180; L-25 to V-179; L-25 to T-178; L-25 to P-177; L-25 to Q-176; L-25 to P-175; L-25 to F-174; L-25 to W-173; L-25 to R-172; L-25 to P-171; L-25 to A-170; L-25 to E-169; L-25 to C-168; L-25 to R-167; L-25 to L-166; L-25 to T-165; L-25 to E-164; L-25 to S-163; L-25 to S-162; L-25 to A-161; L-25 to N-160; L-25 to Y-159; L-25 to D-158; L-25 to V-157; L-25 to N-156; L-25 to V-155; L-25 to E-154; L-25 to P-153; L-25 to M-152; L-25 to S-151; L-25 to F-150; L-25 to A-149; L-25 to G-148; L-25 to T-147; L-25 to K-146; L-25 to Y-145; L-25 to E-144; L-25 to L-143; L-25 to N-142; L-25 to A-141; L-25 to N-140; L-25 to G-139; L-25 to K-138; L-25 to G-137; L-25 to K-136; L-25 to S-135; L-25 to T-134; L-25 to I-133; L-25 to I-132; L-25 to Y-131; L-25 to C-130; L-25 to K-129; L-25 to Y-128; L-25 to T-127; L-25 to G-126; L-25 to A-125; L-25 to D-124; L-25 to T-123; L-25 to L-122; L-25 to Q-121; L-25 to V-120; L-25 to N-119; L-25 to K-118; L-25 to L-117; L-25 to R-116; L-25 to L-115; L-25 to S-114; L-25 to A-113; L-25 to N-112; L-25 to G-111; L-25 to V-110; L-25 to I-109; L-25 to V-108; L-25 to Q-107; L-25 to D-106; L-25 to A-105; L-25 to F-104; L-25 to V-103; L-25 to A-102; L-25 to T-101; L-25 to R-100; L-25 to G-99; L-25 to R-98; L-25 to F-97; L-25 to M-96; L-25 to E-95; L-25 to D-94; L-25 to Q-93; L-25 to E-92; L-25 to S-91; L-25 to L-90; L-25 to E-89; L-25 to D-88; L-25 to K-87; L-25 to G-86; L-25 to E-85; L-25 to K-84; L-25 to F-83; L-25 to E-82; L-25 to H-81; L-25 to V-80; L-25 to L-79; L-25 to G-78; L-25 to L-77; L-25 to V-76; L-25 to G-75; L-25 to E-74; L-25 to K-73; L-25 to L-72; L-25 to W-71; L-25 to Q-70; L-25 to I-69; L-25 to V-68; L-25 to I-67; L-25 to D-66; L-25 to S-65; L-25 to L-64; L-25 to K-63; L-25 to I-62; L-25 to D-61; L-25 to P-60; L-25 to E-59; L-25 to F-58; L-25 to T-57; L-25 to C-56; L-25 to S-55; L-25 to L-54; L-25 to I-53; L-25 to G-52; L-25 to D-51; L-25 to E-50; L-25 to G-49; L-25 to I-48; L-25 to N-47; L-25 to G-46; L-25 to A-45; L-25 to S-44; L-25 to A-43; L-25 to V-42; L-25 to T-41; L-25 to T-40; L-25 to V-39; L-25 to T-38; L-25 to I-37; L-25 to S-36; L-25 to H-35; L-25 to R-

34; L-25 to G-33; L-25 to S-32; and/or L-25 to I-31 of SEQ ID NO: 14. Polynucleotides encoding these polypeptides are also encompassed by the invention, as are antibodies that bind one or more of these polypeptides. Moreover, fragments and variants of these polypeptides (e.g., fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof) are encompassed by the invention. Antibodies that bind these fragments and variants of the invention are also encompassed by the invention. Polynucleotides encoding these fragments and variants are also encompassed by the invention.

[75] In addition, any of the above listed N- or C-terminal deletions can be combined to produce a N- and C-terminal deleted polypeptide. The invention also provides polypeptides comprising, or alternatively consisting of, one or more amino acids deleted from both the amino and the carboxyl termini, which may be described generally as having residues m-n of SEQ ID NO: 14, where n and m are integers as described above. Fragments and/or variants of these polypeptides, such as, for example, fragments and/or variants as described herein, are encompassed by the invention. Polynucleotides encoding these polypeptides (including fragments and/or variants) are also encompassed by the invention, as are antibodies that bind these polypeptides.

[76] The present invention is also directed to proteins containing polypeptides at least 80%, 85%, 90%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to a polypeptide sequence set forth herein as m-n. In preferred embodiments, the application is directed to proteins containing polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to polypeptides having the amino acid sequence of the specific N- and C-terminal deletions recited herein. Fragments and/or variants of these polypeptides, such as, for example, fragments and/or variants as described herein, are encompassed by the invention. Polynucleotides encoding these polypeptides (including fragments and/or variants) are also encompassed by the invention, as are antibodies that bind these polypeptides.

[77] Also included are polynucleotide sequences encoding a polypeptide consisting of a portion of the complete amino acid sequence encoded by a cDNA clone contained in ATCC Deposit No. PTA-2332, where this portion excludes any integer of amino acid residues from 1 to about 276 amino acids from the amino terminus of the complete amino acid sequence

encoded by a cDNA clone contained in ATCC Deposit No. PTA-2332, or any integer of amino acid residues from 1 to about 276 amino acids from the carboxy terminus, or any combination of the above amino terminal and carboxy terminal deletions, of the complete amino acid sequence encoded by the cDNA clone contained in ATCC Deposit No. PTA-2332. Polypeptides encoded by these polynucleotides also are encompassed by the invention.

[78] As described herein or otherwise known in the art, the polynucleotides of the invention have uses that include, but are not limited to, serving as probes or primers in chromosome identification, chromosome mapping, and linkage analysis.

[79] It has been discovered that this gene is expressed in dendritic cells, T cells, and infant brain tissue.

[80] Polynucleotides, translation products and antibodies corresponding to this gene are useful as reagents for differential identification of immune system tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases and/or disorders involving immune system activation, stimulation and/or surveillance, particularly involving T cells, in addition to other immune system cells such as dendritic cells, neutrophils, and leukocytes, as well as for diseases and/or disorders of the neural system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). Particularly contemplated are the use of antibodies directed against the extracellular portion of this protein which act as antagonists for the activity of the B7-H8 protein. Such antagonistic antibodies would be useful for the prevention and/or inhibition of such biological activites as are disclosed herein (e.g. T cell modulated activities).

[81] For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, neural, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

[82] The tissue distribution in immune cells (e.g., T-cells, dendritic cells), and the homology to members of the B7 family of ligands, indicates that the polynucleotides, translation products and antibodies corresponding to this gene are useful for the diagnosis,

detection and/or treatment of diseases and/or disorders involving immune system activation, stimulation and/or surveillance, particularly as relating to T cells, neutrophils, dendritic cells, leukocytes, and other immune system cells. In particular, the translation product of the B7-H8 gene may be involved in the costimulation of T cells, binding to ICOS, and/or may play a role in modulation of the expression of particular cytokines, for example.

[83] More generally, the tissue distribution in immune system cells indicates that this gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of immune system origin, polynucleotides, translation products and antibodies corresponding to this gene may show utility as a tumor marker and/or immunotherapy targets for immune system cells and tissues.

[84] Polynucleotides, translation products and antibodies corresponding to this gene may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement.

[85] Expression within infant brain tissue suggests that polynucleotides, translation products and antibodies corresponding to this clone are useful for the detection and/or treatment of neurodegenerative disease states and behavioural disorders such as Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders. Additionally, polynucleotides, translation products and antibodies corresponding to this gene may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 2

[86] For purposes of this application, this gene and its corresponding translation product are known as the B7-H7 gene and B7-H7 protein. This protein is believed to reside as a cell-surface molecule, and the transmembrane domain of this protein is believed to approximately embody the following preferred amino acid residues: PTWLLHIFIPSCIIAFIFIATVIALRKQLC (SEQ ID NO: 30). Polynucleotides encoding these polypeptides are also encompassed by the invention, as are antibodies that bind one or more of these peptides. As one skilled in the art would understand, the transmembrane domain was predicted using computer analysis, and the transmembrane domain may vary by one, two, three, four, five, six, seven, eight, nine, and/or ten amino acids from the N and C-termini of the predicted transmembrane domain.

[87] The B7-H7 gene shares sequence homology with members of the B7 family of ligands (i.e., B7-H1 (See Genbank Accession AAF25807)). These proteins and their corresponding receptors play vital roles in the growth, differentiation, activation, proliferation and death of T cells. For example, some members of this family (i.e., B7-H1) are involved in costimulation of the T cell response, as well as inducing increased cytokine production, while other family members are involved in the negative regulation of the T cell response. Therefore, agonists and antagonists such as antibodies or small molecules directed against the B7-H7 gene are useful for treating T cell mediated immune system disorders, as well as disorders of other immune system cells, such as for example, neutrophils, macrophage, and leukocytes.

[88] Preferred polypeptides of the present invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, or all seven of the immunogenic epitopes of the B7-H7 protein shown in SEQ ID NO: 15 as residues: Lys-61 to Arg-72, Arg-95 to Tyr-100, Ala-121 to Ile-126, Asn-163 to Gly-172, Lys-183 to Asn-189, Ser-211 to His-218, and Leu-251 to Val-269. Polynucleotides encoding these polypeptides are also encompassed by the invention, as are antibodies that bind one or more of these polypeptides. Moreover, fragments and variants of these polypeptides (e.g., fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof) are encompassed by the invention. Antibodies that bind these fragments and variants of the invention are also

encompassed by the invention. Polynucleotides encoding these fragments and variants are also encompassed by the invention.

[89] In additional nonexclusive embodiments, polypeptides of the invention comprise, or alternatively consist of, an amino acid sequence selected from the group consisting of:

[90] The extracellular domain of the B7-H7 protein: MIFLLLMLSLELQLHQIAALFTVTVPKELYIIEHGSNVTLECNFDTGSHVNLGAITASLQKVENDTSPHRERATLLEEQLPLGKASFHIPQVQVRDEGQYQCIIIYGVAWDYKYLTLKVKASYRKINTHILKVPETDEVELTCQATGYPLAEVSWPNVSVPANTSHSRTPEGLYQVTSVLRLKPPPGRNFSCVFWNTHVRELTLASIDLQSQMEPRTH (SEQ ID NO: 31),

[91] The mature extracellular domain of the B7-H7 protein: LFTVTVPKELYIIEHGSNVTLECNFDTGSHVNLGAITASLQKVENDTSPHRERATLLEEQLPLGKASFHIPQVQVRDEGQYQCIIIYGVAWDYKYLTLKVKASYRKINTHILKVPETDEVELTCQATGYPLAEVSWPNVSVPANTSHSRTPEGLYQVTSVLRLKPPPGRNFSCVFWNTHVRELTLASIDLQSQMEPRTH (SEQ ID NO: 32), and/or

[92] The leader sequence of the B7-H7 protein: MIFLLLMLSLELQLHQIAA (SEQ ID NO: 33).

[93] Polynucleotides encoding these polypeptides are also encompassed by the invention, as are antibodies that bind one or more of these polypeptides. Moreover, fragments and variants of these polypeptides (e.g., fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof) are encompassed by the invention. Antibodies that bind these fragments and variants of the invention are also encompassed by the invention. Polynucleotides encoding these fragments and variants are also encompassed by the invention.

[94] In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, an amino acid sequence selected from the pair of immunoglobulin-like regions of the B7-H7 protein:
ELYIIEHGSNVTLECNFDTGSHVNLGAITASLQKVENDTSPHRERATLLEEQLPLGKASFHIPQVQVRDEGQYQCIIIYGVAWDYKYLTLKVK (SEQ ID NO: 34) and/or
SYRKINTHILKVPETDEVELTCQATGYPLAEVSWPNVSVPANTSHSRTPEGLYQVTSVLRLKPPPGRNFSCVFWNTHVRELTLASIDLQSQMEP (SEQ ID NO: 35). Polynucleotides

encoding these polypeptides are also encompassed by the invention, as are antibodies that bind one or more of these polypeptides. Moreover, fragments and variants of these polypeptides (e.g., fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof) are encompassed by the invention. Antibodies that bind these fragments and variants of the invention are also encompassed by the invention. Polynucleotides encoding these fragments and variants are also encompassed by the invention.

[95] Also preferred are polypeptides comprising, or alternatively consisting of, fragments of the mature extracellular portion of the B7-H7 protein demonstrating functional activity (SEQ ID NO: 32). Fragments and/or variants of these polypeptides, such as, for example, fragments and/or variants as described herein, are encompassed by the invention. Polynucleotides encoding these polypeptides (including fragments and/or variants) are also encompassed by the invention, as are antibodies that bind these polypeptides.

[96] By functional activity is meant, a polypeptide fragment capable of displaying one or more known functional activities associated with the full-length (complete) B7-H7 protein. Such functional activities include, but are not limited to, biological activity (e.g., T cell costimulatory activity, ability to bind ICOS, CD28 or CTLA4, and ability to induce or inhibit cytokine production), antigenicity [ability to bind (or compete with a B7-H7 polypeptide for binding) to an anti-B7-H7 antibody], immunogenicity (ability to generate antibody which binds to a B7-H7 polypeptide), ability to form multimers with B7-H7 polypeptides of the invention, and ability to bind to a receptor for a B7-H7 polypeptide.

[97] Figures 3A-C show the nucleotide (SEQ ID NO: 3) and deduced amino acid sequence (SEQ ID NO: 15) corresponding to this gene.

[98] Figure 4 shows an analysis of the amino acid sequence (SEQ ID NO: 15). Alpha, beta, turn and coil regions; hydrophilicity and hydrophobicity; amphipathic regions; flexible regions; antigenic index and surface probability are shown, and all were generated using the default settings of the recited computer algorithyms. In the "Antigenic Index or Jameson-Wolf" graph, the positive peaks indicate locations of the highly antigenic regions of the protein, i.e., regions from which epitope-bearing peptides of the invention can be obtained. Polypeptides comprising, or alternatively consisting of, domains defined by these graphs are

contemplated by the present invention, as are polynucleotides encoding these polypeptides. The data presented in Figure 4 are also represented in tabular form in Table 4. The columns are labeled with the headings "Res", "Position", and Roman Numerals I-XIV. The column headings refer to the following features of the amino acid sequence presented in Figure 4, and Table 4: "Res": amino acid residue of SEQ ID NO: 15 and Figures 3A-C; "Position": position of the corresponding residue within SEQ ID NO: 15 and Figures 3A-C; I: Alpha, Regions - Garnier-Robson; II: Alpha, Regions - Chou-Fasman; III: Beta, Regions - Garnier-Robson; IV: Beta, Regions - Chou-Fasman; V: Turn, Regions - Garnier-Robson; VI: Turn, Regions - Chou-Fasman; VII: Coil, Regions - Garnier-Robson; VIII: Hydrophilicity Plot - Kyte-Doolittle; IX: Hydrophobicity Plot - Hopp-Woods; X: Alpha, Amphipathic Regions - Eisenberg; XI: Beta, Amphipathic Regions - Eisenberg; XII: Flexible Regions - Karplus-Schulz; XIII: Antigenic Index - Jameson-Wolf; and XIV: Surface Probability Plot - Emini. Preferred embodiments of the invention in this regard include fragments that comprise, or alternatively consisting of, one or more of the following regions: alpha-helix and alpha-helix forming regions ("alpha-regions"), beta-sheet and beta-sheet forming regions ("beta-regions"), turn and turn-forming regions ("turn-regions"), coil and coil-forming regions ("coil-regions"), hydrophilic regions, hydrophobic regions, alpha amphipathic regions, beta amphipathic regions, flexible regions, surface-forming regions and high antigenic index regions. The data representing the structural or functional attributes of the protein set forth in Figure 4 and/or Table 4, as described above, was generated using the various modules and algorithms of the DNA*STAR set on default parameters. In a preferred embodiment, the data presented in columns VIII, IX, XIII, and XIV of Table 4 can be used to determine regions of the protein which exhibit a high degree of potential for antigenicity. Regions of high antigenicity are determined from the data presented in columns VIII, IX, XIII, and/or XIV by choosing values which represent regions of the polypeptide which are likely to be exposed on the surface of the polypeptide in an environment in which antigen recognition may occur in the process of initiation of an immune response. Certain preferred regions in these regards are set out in Figure 4, but may, as shown in Table 4, be represented or identified by using tabular representations of the data presented in Figure 4. The DNA*STAR computer algorithm used to generate Figure 4 (set on the original default parameters) was used to present the data in Figure 4 in a tabular format (See Table 4). The tabular format of the data

in Figure 4 (See Table 4) is used to easily determine specific boundaries of a preferred region.

[99] The present invention is further directed to fragments of the polynucleotide sequences described herein. By a fragment of, for example, the polynucleotide sequence of a deposited cDNA or the nucleotide sequence shown in SEQ ID NO: 3, is intended polynucleotide fragments at least about 15nt, and more preferably at least about 20 nt, at least about 25nt, still more preferably at least about 30 nt, at least about 35nt, and even more preferably, at least about 40 nt in length, at least about 45nt in length, at least about 50nt in length, at least about 60nt in length, at least about 70nt in length, at least about 80nt in length, at least about 90nt in length, at least about 100nt in length, at least about 125nt in length, at least about 150nt in length, at least about 175nt in length, which are useful as diagnostic probes and primers as discussed herein. Of course, larger fragments 200-1500 nt in length are also useful according to the present invention, as are fragments corresponding to most, if not all, of the nucleotide sequence of a deposited cDNA or as shown in SEQ ID NO: 3. By a fragment at least 20 nt in length, for example, is intended fragments which include 20 or more contiguous bases from the nucleotide sequence of a deposited cDNA or the nucleotide sequence as shown in SEQ ID NO: 3. In this context "about" includes the particularly recited size, an sizes larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Representative examples of polynucleotide fragments of the invention include, for example, fragments that comprise, or alternatively, consist of, a sequence from about nucleotide 1 to about 50, from about 51 to about 100, from about 101 to about 150, from about 151 to about 200, from about 201 to about 250, from about 251 to about 300, from about 301 to about 350, from about 351 to about 400, from about 401 to about 450, from about 451 to about 500, and from about 501 to about 550, and from about 551 to about 600, from about 601 to about 650, from about 651 to about 700, from about 701 to about 750, from about 751 to about 800, and from about 801 to about 860, of SEQ ID NO: 3, or the complementary strand thereto, or the cDNA contained in a deposited clone. In this context "about" includes the particularly recited ranges, and ranges larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. In additional embodiments, the polynucleotides of the invention encode functional attributes of the corresponding protein.

[100] Preferred polypeptide fragments of the invention comprise, or alternatively consist of, the secreted protein having a continuous series of deleted residues from the amino or the

carboxy terminus, or both. Particularly, N-terminal deletions of the polypeptide can be described by the general formula m-283 where m is an integer from 2 to 278, where m corresponds to the position of the amino acid residue identified in SEQ ID NO: 15. More in particular, the invention provides polynucleotides encoding polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group: I-2 to G-283; F-3 to G-283; L-4 to G-283; L-5 to G-283; L-6 to G-283; M-7 to G-283; L-8 to G-283; S-9 to G-283; L-10 to G-283; E-11 to G-283; L-12 to G-283; Q-13 to G-283; L-14 to G-283; H-15 to G-283; Q-16 to G-283; I-17 to G-283; A-18 to G-283; A-19 to G-283; L-20 to G-283; F-21 to G-283; T-22 to G-283; V-23 to G-283; T-24 to G-283; V-25 to G-283; P-26 to G-283; K-27 to G-283; E-28 to G-283; L-29 to G-283; Y-30 to G-283; I-31 to G-283; I-32 to G-283; E-33 to G-283; H-34 to G-283; G-35 to G-283; S-36 to G-283; N-37 to G-283; V-38 to G-283; T-39 to G-283; L-40 to G-283; E-41 to G-283; C-42 to G-283; N-43 to G-283; F-44 to G-283; D-45 to G-283; T-46 to G-283; G-47 to G-283; S-48 to G-283; H-49 to G-283; V-50 to G-283; N-51 to G-283; L-52 to G-283; G-53 to G-283; A-54 to G-283; I-55 to G-283; T-56 to G-283; A-57 to G-283; S-58 to G-283; L-59 to G-283; Q-60 to G-283; K-61 to G-283; V-62 to G-283; E-63 to G-283; N-64 to G-283; D-65 to G-283; T-66 to G-283; S-67 to G-283; P-68 to G-283; H-69 to G-283; R-70 to G-283; E-71 to G-283; R-72 to G-283; A-73 to G-283; T-74 to G-283; L-75 to G-283; L-76 to G-283; E-77 to G-283; E-78 to G-283; Q-79 to G-283; L-80 to G-283; P-81 to G-283; L-82 to G-283; G-83 to G-283; K-84 to G-283; A-85 to G-283; S-86 to G-283; F-87 to G-283; H-88 to G-283; I-89 to G-283; P-90 to G-283; Q-91 to G-283; V-92 to G-283; Q-93 to G-283; V-94 to G-283; R-95 to G-283; D-96 to G-283; E-97 to G-283; G-98 to G-283; Q-99 to G-283; Y-100 to G-283; Q-101 to G-283; C-102 to G-283; I-103 to G-283; I-104 to G-283; I-105 to G-283; Y-106 to G-283; G-107 to G-283; V-108 to G-283; A-109 to G-283; W-110 to G-283; D-111 to G-283; Y-112 to G-283; K-113 to G-283; Y-114 to G-283; L-115 to G-283; T-116 to G-283; L-117 to G-283; K-118 to G-283; V-119 to G-283; K-120 to G-283; A-121 to G-283; S-122 to G-283; Y-123 to G-283; R-124 to G-283; K-125 to G-283; I-126 to G-283; N-127 to G-283; T-128 to G-283; H-129 to G-283; I-130 to G-283; L-131 to G-283; K-132 to G-283; V-133 to G-283; P-134 to G-283; E-135 to G-283; T-136 to G-283; D-137 to G-283; E-138 to G-283; V-139 to G-283; E-140 to G-283; L-141 to G-283; T-142 to G-283; C-143 to G-283; Q-144 to G-283; A-145 to G-283; T-146 to G-283; G-147 to G-283; Y-148 to G-283; P-149 to G-283; L-150 to G-283; A-151 to G-283; E-152 to G-283; V-153 to G-283; S-154 to G-283; W-155 to G-283; P-156 to G-283; N-

157 to G-283; V-158 to G-283; S-159 to G-283; V-160 to G-283; P-161 to G-283; A-162 to G-283; N-163 to G-283; T-164 to G-283; S-165 to G-283; H-166 to G-283; S-167 to G-283; R-168 to G-283; T-169 to G-283; P-170 to G-283; E-171 to G-283; G-172 to G-283; L-173 to G-283; Y-174 to G-283; Q-175 to G-283; V-176 to G-283; T-177 to G-283; S-178 to G-283; V-179 to G-283; L-180 to G-283; R-181 to G-283; L-182 to G-283; K-183 to G-283; P-184 to G-283; P-185 to G-283; P-186 to G-283; G-187 to G-283; R-188 to G-283; N-189 to G-283; F-190 to G-283; S-191 to G-283; C-192 to G-283; V-193 to G-283; F-194 to G-283; W-195 to G-283; N-196 to G-283; T-197 to G-283; H-198 to G-283; V-199 to G-283; R-200 to G-283; E-201 to G-283; L-202 to G-283; T-203 to G-283; L-204 to G-283; A-205 to G-283; S-206 to G-283; I-207 to G-283; D-208 to G-283; L-209 to G-283; Q-210 to G-283; S-211 to G-283; Q-212 to G-283; M-213 to G-283; E-214 to G-283; P-215 to G-283; R-216 to G-283; T-217 to G-283; H-218 to G-283; P-219 to G-283; T-220 to G-283; W-221 to G-283; L-222 to G-283; L-223 to G-283; H-224 to G-283; I-225 to G-283; F-226 to G-283; I-227 to G-283; P-228 to G-283; S-229 to G-283; C-230 to G-283; I-231 to G-283; I-232 to G-283; A-233 to G-283; F-234 to G-283; I-235 to G-283; F-236 to G-283; I-237 to G-283; A-238 to G-283; T-239 to G-283; V-240 to G-283; I-241 to G-283; A-242 to G-283; L-243 to G-283; R-244 to G-283; K-245 to G-283; Q-246 to G-283; L-247 to G-283; C-248 to G-283; Q-249 to G-283; K-250 to G-283; L-251 to G-283; Y-252 to G-283; S-253 to G-283; S-254 to G-283; K-255 to G-283; D-256 to G-283; T-257 to G-283; T-258 to G-283; K-259 to G-283; R-260 to G-283; P-261 to G-283; V-262 to G-283; T-263 to G-283; T-264 to G-283; T-265 to G-283; K-266 to G-283; R-267 to G-283; E-268 to G-283; V-269 to G-283; N-270 to G-283; S-271 to G-283; A-272 to G-283; V-273 to G-283; N-274 to G-283; L-275 to G-283; N-276 to G-283; L-277 to G-283; and/or W-278 to G-283 of SEQ ID NO: 15. Polynucleotides encoding these polypeptides are also encompassed by the invention, as are antibodies that bind one or more of these polypeptides. Moreover, fragments and variants of these polypeptides (e.g., fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof) are encompassed by the invention. Antibodies that bind these fragments and variants of the invention are also encompassed by the invention. Polynucleotides encoding these fragments and variants are also encompassed by the invention.

[101] Accordingly, the present invention further provides polypeptides having one or more residues deleted from the carboxy terminus of the amino acid sequence of the polypeptide shown in Figures 3A-C (SEQ ID NO: 15), as described by the general formula 1-n, where n is an integer from 7 to 282, where n corresponds to the position of the amino acid residue identified in SEQ ID NO: 15. Additionally, the invention provides polynucleotides encoding polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the following group of C-terminal deletions: M-1 to P-282; M-1 to E-281; M-1 to W-280; M-1 to S-279; M-1 to W-278; M-1 to L-277; M-1 to N-276; M-1 to L-275; M-1 to N-274; M-1 to V-273; M-1 to A-272; M-1 to S-271; M-1 to N-270; M-1 to V-269; M-1 to E-268; M-1 to R-267; M-1 to K-266; M-1 to T-265; M-1 to T-264; M-1 to T-263; M-1 to V-262; M-1 to P-261; M-1 to R-260; M-1 to K-259; M-1 to T-258; M-1 to T-257; M-1 to D-256; M-1 to K-255; M-1 to S-254; M-1 to S-253; M-1 to Y-252; M-1 to L-251; M-1 to K-250; M-1 to Q-249; M-1 to C-248; M-1 to L-247; M-1 to Q-246; M-1 to K-245; M-1 to R-244; M-1 to L-243; M-1 to A-242; M-1 to I-241; M-1 to V-240; M-1 to T-239; M-1 to A-238; M-1 to I-237; M-1 to F-236; M-1 to I-235; M-1 to F-234; M-1 to A-233; M-1 to I-232; M-1 to I-231; M-1 to C-230; M-1 to S-229; M-1 to P-228; M-1 to I-227; M-1 to F-226; M-1 to I-225; M-1 to H-224; M-1 to L-223; M-1 to L-222; M-1 to W-221; M-1 to T-220; M-1 to P-219; M-1 to H-218; M-1 to T-217; M-1 to R-216; M-1 to P-215; M-1 to E-214; M-1 to M-213; M-1 to Q-212; M-1 to S-211; M-1 to Q-210; M-1 to L-209; M-1 to D-208; M-1 to I-207; M-1 to S-206; M-1 to A-205; M-1 to L-204; M-1 to T-203; M-1 to L-202; M-1 to E-201; M-1 to R-200; M-1 to V-199; M-1 to H-198; M-1 to T-197; M-1 to N-196; M-1 to W-195; M-1 to F-194; M-1 to V-193; M-1 to C-192; M-1 to S-191; M-1 to F-190; M-1 to N-189; M-1 to R-188; M-1 to G-187; M-1 to P-186; M-1 to P-185; M-1 to P-184; M-1 to K-183; M-1 to L-182; M-1 to R-181; M-1 to L-180; M-1 to V-179; M-1 to S-178; M-1 to T-177; M-1 to V-176; M-1 to Q-175; M-1 to Y-174; M-1 to L-173; M-1 to G-172; M-1 to E-171; M-1 to P-170; M-1 to T-169; M-1 to R-168; M-1 to S-167; M-1 to H-166; M-1 to S-165; M-1 to T-164; M-1 to N-163; M-1 to A-162; M-1 to P-161; M-1 to V-160; M-1 to S-159; M-1 to V-158; M-1 to N-157; M-1 to P-156; M-1 to W-155; M-1 to S-154; M-1 to V-153; M-1 to E-152; M-1 to A-151; M-1 to L-150; M-1 to P-149; M-1 to Y-148; M-1 to G-147; M-1 to T-146; M-1 to A-145; M-1 to Q-144; M-1 to C-143; M-1 to T-142; M-1 to L-141; M-1 to E-140; M-1 to V-139; M-1 to E-138; M-1 to D-137; M-1 to T-136; M-1 to E-135; M-1 to P-134; M-1 to V-133; M-1 to K-132; M-1 to L-131; M-1 to I-130; M-1 to H-129; M-1 to T-

128; M-1 to N-127; M-1 to I-126; M-1 to K-125; M-1 to R-124; M-1 to Y-123; M-1 to S-122; M-1 to A-121; M-1 to K-120; M-1 to V-119; M-1 to K-118; M-1 to L-117; M-1 to T-116; M-1 to L-115; M-1 to Y-114; M-1 to K-113; M-1 to Y-112; M-1 to D-111; M-1 to W-110; M-1 to A-109; M-1 to V-108; M-1 to G-107; M-1 to Y-106; M-1 to I-105; M-1 to I-104; M-1 to I-103; M-1 to C-102; M-1 to Q-101; M-1 to Y-100; M-1 to Q-99; M-1 to G-98; M-1 to E-97; M-1 to D-96; M-1 to R-95; M-1 to V-94; M-1 to Q-93; M-1 to V-92; M-1 to Q-91; M-1 to P-90; M-1 to I-89; M-1 to H-88; M-1 to F-87; M-1 to S-86; M-1 to A-85; M-1 to K-84; M-1 to G-83; M-1 to L-82; M-1 to P-81; M-1 to L-80; M-1 to Q-79; M-1 to E-78; M-1 to E-77; M-1 to L-76; M-1 to L-75; M-1 to T-74; M-1 to A-73; M-1 to R-72; M-1 to E-71; M-1 to R-70; M-1 to H-69; M-1 to P-68; M-1 to S-67; M-1 to T-66; M-1 to D-65; M-1 to N-64; M-1 to E-63; M-1 to V-62; M-1 to K-61; M-1 to Q-60; M-1 to L-59; M-1 to S-58; M-1 to A-57; M-1 to T-56; M-1 to I-55; M-1 to A-54; M-1 to G-53; M-1 to L-52; M-1 to N-51; M-1 to V-50; M-1 to H-49; M-1 to S-48; M-1 to G-47; M-1 to T-46; M-1 to D-45; M-1 to F-44; M-1 to N-43; M-1 to C-42; M-1 to E-41; M-1 to L-40; M-1 to T-39; M-1 to V-38; M-1 to N-37; M-1 to S-36; M-1 to G-35; M-1 to H-34; M-1 to E-33; M-1 to I-32; M-1 to I-31; M-1 to Y-30; M-1 to L-29; M-1 to E-28; M-1 to K-27; M-1 to P-26; M-1 to V-25; M-1 to T-24; M-1 to V-23; M-1 to T-22; M-1 to F-21; M-1 to L-20; M-1 to A-19; M-1 to A-18; M-1 to I-17; M-1 to Q-16; M-1 to H-15; M-1 to L-14; M-1 to Q-13; M-1 to L-12; M-1 to E-11; M-1 to L-10; M-1 to S-9; M-1 to L-8; and/or M-1 to M-7 of SEQ ID NO: 15. Polynucleotides encoding these polypeptides are also encompassed by the invention, as are antibodies that bind one or more of these polypeptides. Moreover, fragments and variants of these polypeptides (e.g., fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof) are encompassed by the invention. Antibodies that bind these fragments and variants of the invention are also encompassed by the invention. Polynucleotides encoding these fragments and variants are also encompassed by the invention.

[102] Also as mentioned above, even if deletion of one or more amino acids from the C-terminus of a protein results in modification of loss of one or more biological functions of the protein (e.g., ability to inhibit the Mixed Lymphocyte Reaction), other functional activities (e.g., biological activities, ability to multimerize, ability to bind receptor, ability to generate

antibodies, ability to bind antibodies) may still be retained. For example, the ability of the shortened polypeptide to induce and/or bind to antibodies which recognize the complete or mature forms of the polypeptide generally will be retained when less than the majority of the residues of the complete or mature polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a polypeptide with a large number of deleted C-terminal amino acid residues may retain some biological or immunogenic activities. In fact, peptides composed of as few as six amino acid residues may often evoke an immune response.

[103] More in particular, the invention provides polynucleotides encoding polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group of N-terminal deletions of the mature extracellular portion of the B7-H7 protein (SEQ ID NO: 32): F-21 to H-218; T-22 to H-218; V-23 to H-218; T-24 to H-218; V-25 to H-218; P-26 to H-218; K-27 to H-218; E-28 to H-218; L-29 to H-218; Y-30 to H-218; I-31 to H-218; I-32 to H-218; E-33 to H-218; H-34 to H-218; G-35 to H-218; S-36 to H-218; N-37 to H-218; V-38 to H-218; T-39 to H-218; L-40 to H-218; E-41 to H-218; C-42 to H-218; N-43 to H-218; F-44 to H-218; D-45 to H-218; T-46 to H-218; G-47 to H-218; S-48 to H-218; H-49 to H-218; V-50 to H-218; N-51 to H-218; L-52 to H-218; G-53 to H-218; A-54 to H-218; I-55 to H-218; T-56 to H-218; A-57 to H-218; S-58 to H-218; L-59 to H-218; Q-60 to H-218; K-61 to H-218; V-62 to H-218; E-63 to H-218; N-64 to H-218; D-65 to H-218; T-66 to H-218; S-67 to H-218; P-68 to H-218; H-69 to H-218; R-70 to H-218; E-71 to H-218; R-72 to H-218; A-73 to H-218; T-74 to H-218; L-75 to H-218; L-76 to H-218; E-77 to H-218; E-78 to H-218; Q-79 to H-218; L-80 to H-218; P-81 to H-218; L-82 to H-218; G-83 to H-218; K-84 to H-218; A-85 to H-218; S-86 to H-218; F-87 to H-218; H-88 to H-218; I-89 to H-218; P-90 to H-218; Q-91 to H-218; V-92 to H-218; Q-93 to H-218; V-94 to H-218; R-95 to H-218; D-96 to H-218; E-97 to H-218; G-98 to H-218; Q-99 to H-218; Y-100 to H-218; Q-101 to H-218; C-102 to H-218; I-103 to H-218; I-104 to H-218; I-105 to H-218; Y-106 to H-218; G-107 to H-218; V-108 to H-218; A-109 to H-218; W-110 to H-218; D-111 to H-218; Y-112 to H-218; K-113 to H-218; Y-114 to H-218; L-115 to H-218; T-116 to H-218; L-117 to H-218; K-118 to H-218; V-119 to H-218; K-120 to H-218; A-121 to H-218; S-122 to H-218; Y-123 to H-218; R-124 to H-218; K-125 to H-218; I-126 to H-218; N-127 to H-218; T-128 to H-218; H-

129 to H-218; I-130 to H-218; L-131 to H-218; K-132 to H-218; V-133 to H-218; P-134 to H-218; E-135 to H-218; T-136 to H-218; D-137 to H-218; E-138 to H-218; V-139 to H-218; E-140 to H-218; L-141 to H-218; T-142 to H-218; C-143 to H-218; Q-144 to H-218; A-145 to H-218; T-146 to H-218; G-147 to H-218; Y-148 to H-218; P-149 to H-218; L-150 to H-218; A-151 to H-218; E-152 to H-218; V-153 to H-218; S-154 to H-218; W-155 to H-218; P-156 to H-218; N-157 to H-218; V-158 to H-218; S-159 to H-218; V-160 to H-218; P-161 to H-218; A-162 to H-218; N-163 to H-218; T-164 to H-218; S-165 to H-218; H-166 to H-218; S-167 to H-218; R-168 to H-218; T-169 to H-218; P-170 to H-218; E-171 to H-218; G-172 to H-218; L-173 to H-218; Y-174 to H-218; Q-175 to H-218; V-176 to H-218; T-177 to H-218; S-178 to H-218; V-179 to H-218; L-180 to H-218; R-181 to H-218; L-182 to H-218; K-183 to H-218; P-184 to H-218; P-185 to H-218; P-186 to H-218; G-187 to H-218; R-188 to H-218; N-189 to H-218; F-190 to H-218; S-191 to H-218; C-192 to H-218; V-193 to H-218; F-194 to H-218; W-195 to H-218; N-196 to H-218; T-197 to H-218; H-198 to H-218; V-199 to H-218; R-200 to H-218; E-201 to H-218; L-202 to H-218; T-203 to H-218; L-204 to H-218; A-205 to H-218; S-206 to H-218; I-207 to H-218; D-208 to H-218; L-209 to H-218; Q-210 to H-218; S-211 to H-218; Q-212 to H-218; and/or M-213 to H-218 of SEQ ID NO: 15. Polynucleotides encoding these polypeptides are also encompassed by the invention, as are antibodies that bind one or more of these polypeptides. Moreover, fragments and variants of these polypeptides (e.g., fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof) are encompassed by the invention. Antibodies that bind these fragments and variants of the invention are also encompassed by the invention. Polynucleotides encoding these fragments and variants are also encompassed by the invention.

[104] Additionally, the invention provides polynucleotides encoding polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group of C-terminal deletions of the mature extracellular portion of the B7-H7 protein (SEQ ID NO: 32): L-20 to T-217; L-20 to R-216; L-20 to P-215; L-20 to E-214; L-20 to M-213; L-20 to Q-212; L-20 to S-211; L-20 to Q-210; L-20 to L-209; L-20 to D-208; L-20 to I-207; L-20 to S-206; L-20 to A-205; L-20 to L-204; L-20 to T-203; L-20 to L-202; L-20 to E-201; L-20 to R-200; L-20 to V-199; L-20 to H-198; L-20 to T-197; L-20 to N-196; L-20 to W-195; L-20 to

F-194; L-20 to V-193; L-20 to C-192; L-20 to S-191; L-20 to F-190; L-20 to N-189; L-20 to R-188; L-20 to G-187; L-20 to P-186; L-20 to P-185; L-20 to P-184; L-20 to K-183; L-20 to L-182; L-20 to R-181; L-20 to L-180; L-20 to V-179; L-20 to S-178; L-20 to T-177; L-20 to V-176; L-20 to Q-175; L-20 to Y-174; L-20 to L-173; L-20 to G-172; L-20 to E-171; L-20 to P-170; L-20 to T-169; L-20 to R-168; L-20 to S-167; L-20 to H-166; L-20 to S-165; L-20 to T-164; L-20 to N-163; L-20 to A-162; L-20 to P-161; L-20 to V-160; L-20 to S-159; L-20 to V-158; L-20 to N-157; L-20 to P-156; L-20 to W-155; L-20 to S-154; L-20 to V-153; L-20 to E-152; L-20 to A-151; L-20 to L-150; L-20 to P-149; L-20 to Y-148; L-20 to G-147; L-20 to T-146; L-20 to A-145; L-20 to Q-144; L-20 to C-143; L-20 to T-142; L-20 to L-141; L-20 to E-140; L-20 to V-139; L-20 to E-138; L-20 to D-137; L-20 to T-136; L-20 to E-135; L-20 to P-134; L-20 to V-133; L-20 to K-132; L-20 to L-131; L-20 to I-130; L-20 to H-129; L-20 to T-128; L-20 to N-127; L-20 to I-126; L-20 to K-125; L-20 to R-124; L-20 to Y-123; L-20 to S-122; L-20 to A-121; L-20 to K-120; L-20 to V-119; L-20 to K-118; L-20 to L-117; L-20 to T-116; L-20 to L-115; L-20 to Y-114; L-20 to K-113; L-20 to Y-112; L-20 to D-111; L-20 to W-110; L-20 to A-109; L-20 to V-108; L-20 to G-107; L-20 to Y-106; L-20 to I-105; L-20 to I-104; L-20 to I-103; L-20 to C-102; L-20 to Q-101; L-20 to Y-100; L-20 to Q-99; L-20 to G-98; L-20 to E-97; L-20 to D-96; L-20 to R-95; L-20 to V-94; L-20 to Q-93; L-20 to V-92; L-20 to Q-91; L-20 to P-90; L-20 to I-89; L-20 to H-88; L-20 to F-87; L-20 to S-86; L-20 to A-85; L-20 to K-84; L-20 to G-83; L-20 to L-82; L-20 to P-81; L-20 to L-80; L-20 to Q-79; L-20 to E-78; L-20 to E-77; L-20 to L-76; L-20 to L-75; L-20 to T-74; L-20 to A-73; L-20 to R-72; L-20 to E-71; L-20 to R-70; L-20 to H-69; L-20 to P-68; L-20 to S-67; L-20 to T-66; L-20 to D-65; L-20 to N-64; L-20 to E-63; L-20 to V-62; L-20 to K-61; L-20 to Q-60; L-20 to L-59; L-20 to S-58; L-20 to A-57; L-20 to T-56; L-20 to I-55; L-20 to A-54; L-20 to G-53; L-20 to L-52; L-20 to N-51; L-20 to V-50; L-20 to H-49; L-20 to S-48; L-20 to G-47; L-20 to T-46; L-20 to D-45; L-20 to F-44; L-20 to N-43; L-20 to C-42; L-20 to E-41; L-20 to L-40; L-20 to T-39; L-20 to V-38; L-20 to N-37; L-20 to S-36; L-20 to G-35; L-20 to H-34; L-20 to E-33; L-20 to I-32; L-20 to I-31; L-20 to Y-30; L-20 to L-29; L-20 to E-28; L-20 to K-27; and/or L-20 to P-26 of SEQ ID NO: 15. Polynucleotides encoding these polypeptides are also encompassed by the invention, as are antibodies that bind one or more of these polypeptides. Moreover, fragments and variants of these polypeptides (e.g., fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under

stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof) are encompassed by the invention. Antibodies that bind these fragments and variants of the invention are also encompassed by the invention. Polynucleotides encoding these fragments and variants are also encompassed by the invention.

[105] In addition, any of the above listed N- or C-terminal deletions can be combined to produce a N- and C-terminal deleted polypeptide. The invention also provides polypeptides comprising, or alternatively consisting of, one or more amino acids deleted from both the amino and the carboxyl termini, which may be described generally as having residues m-n of SEQ ID NO: 15, where n and m are integers as described above. Fragments and/or variants of these polypeptides, such as, for example, fragments and/or variants as described herein, are encompassed by the invention.

[106] Polynucleotides encoding these polypeptides (including fragments and/or variants) are also encompassed by the invention, as are antibodies that bind these polypeptides. The present invention is also directed to proteins containing polypeptides at least 80%, 85%, 90%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to a polypeptide sequence set forth herein as m-n. In preferred embodiments, the application is directed to proteins containing polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to polypeptides having the amino acid sequence of the specific N- and C-terminal deletions recited herein. Fragments and/or variants of these polypeptides, such as, for example, fragments and/or variants as described herein, are encompassed by the invention. Polynucleotides encoding these polypeptides (including fragments and/or variants) are also encompassed by the invention, as are antibodies that bind these polypeptides.

[107] Also included are polynucleotide sequences encoding a polypeptide consisting of a portion of the complete amino acid sequence encoded by a cDNA clone contained in ATCC Deposit No. PTA-2332, where this portion excludes any integer of amino acid residues from 1 to about 277 amino acids from the amino terminus of the complete amino acid sequence encoded by a cDNA clone contained in ATCC Deposit No. PTA-2332, or any integer of amino acid residues from 1 to about 277 amino acids from the carboxy terminus, or any combination of the above amino terminal and carboxy terminal deletions, of the complete amino acid sequence encoded by the cDNA clone contained in ATCC Deposit No. PTA-2332. Polypeptides encoded by these polynucleotides also are encompassed by the invention.

[108] As described herein or otherwise known in the art, the polynucleotides of the invention have uses that include, but are not limited to, serving as probes or primers in chromosome identification, chromosome mapping, and linkage analysis.

[109] It has been discovered that this gene is expressed in dendritic cells, T cells, heart, lung, liver, spleen, and lymph node tissues.

[110] Polynucleotides, translation products and antibodies corresponding to this gene are useful as reagents for differential identification of immune system tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases and/or disorders involving immune system activation, stimulation and/or surveillance, particularly involving T cells, in addition to other immune system cells such as dendritic cells, neutrophils, and leukocytes.

[111] Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). Particularly contemplated are the use of antibodies directed against the extracellular portion of this protein which act as antagonists for the activity of the B7-H7 protein. Such antagonistic antibodies would be useful for the prevention and/or inhibition of such biological activites as are disclosed herein (e.g. T cell modulated activities).

[112] For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, neural, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

[113] The tissue distribution in immune cells (e.g., T-cells, dendritic cells), and the homology to members of the B7 family of ligands, indicates that the polynucleotides, translation products and antibodies corresponding to this gene are useful for the diagnosis, detection and/or treatment of diseases and/or disorders involving immune system activation, stimulation and/or surveillance, particularly as relating to T cells, neutrophils, dendritic cells, leukocytes, and other immune system cells. In particular, the translation product of the B7-H7 gene may be involved in the costimulation of T cells, binding to ICOS, and/or may play a role in modulation of the expression of particular cytokines, for example.

[114] More generally, the tissue distribution in immune system cells indicates that this gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of immune origin, polynucleotides, translation products and antibodies corresponding to this gene may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

[115] Polynucleotides, translation products and antibodies corresponding to this gene may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Additionally, polynucleotides, translation products and antibodies corresponding to this gene may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement.

[116] In addition, the tissue distribution in heart and liver tissues indicates that polynucleotides, translation products and antibodies corresponding to this gene are useful for the diagnosis, detection and or treatment of diseases and/or disorders of the cardiovascular and hepatic systems. Expression within heart tissue suggests that polynucleotides, translation products and antibodies corresponding to this clone are useful for the diagnosis and treatment of conditions and pathologies of the cardiovascular system, such as heart disease, restenosis, atherosclerosis, stroke, angina, thrombosis, and wound healing. Expression within liver tissue suggests that polynucleotides, translation products and antibodies corresponding to this clone are useful for the detection and treatment of liver disorders and cancers (e.g., hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells). In addition the expression in fetus would suggest a useful role for the protein product in developmental abnormalities, fetal deficiencies, pre-natal disorders and various would-healing models and/or tissue trauma.

FEATURES OF PROTEIN ENCODED BY GENE NO: 3

[117] For purposes of this application, this gene and its corresponding translation product are known as the B7-H9 gene and B7-H9 protein. The B7-H9 gene shares sequence homology with members of the B7 family of ligands (i.e., B7-1 (See Genbank Accession 507873)). These proteins and their corresponding receptors play vital roles in the growth, differentiation, activation, proliferation, and death of T cells. For example, some members of this family (i.e., B7-H1) are involved in costimulation of the T cell response, as well as inducing increased cytokine production, while other family members are involved in the negative regulation of the T cell response. Therefore, agonists and antagonists such as antibodies or small molecules directed against the B7-H9 gene are useful for treating T cell mediated immune system disorders.

[118] Preferred polypeptides of the present invention comprise, or alternatively consist of, one, two, three, four, five, or all five of the immunogenic epitopes of the B7-H9 protein shown in SEQ ID NO: 16 as residues: Tyr-67 to Pro-74, Ser-117 to Gln-123, Pro-161 to Met-185, Gly-224 to His-242, and Thr-299 to Trp-307. Polynucleotides encoding these polypeptides are also encompassed by the invention, as are antibodies that bind one or more of these polypeptides. Moreover, fragments and variants of these polypeptides (e.g., fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof) are encompassed by the invention. Antibodies that bind these fragments and variants of the invention are also encompassed by the invention. Polynucleotides encoding these fragments and variants are also encompassed by the invention.

[119] In additional nonexclusive embodiments, polypeptides of the invention comprise, or alternatively consist of, one or both of the following amino acid sequences:

[120] The mature region of the B7-H9 protein: QWQVFGPDKPVQALVGEDAAFSCFLSPKTNAEAMEVRFFRGQFSSVVHLYRDGKD QPFMQMPQYQGRTKLVKDSIAEGRISLRLENITVLDAGLYGCRISSQSYYQKAIWEL QVSALGSVPLISIAGYVDRDIQLLCQSSGWFPRPTAKWKGPQGQDLSTDSRTNRDMH GLFDVEISLTVQENAGSISCSMRHAHLSREVESRVQIGDWRRKHGQAGKRKYSSSHI

YDSFPSLSFMDFYILRPVGPCRAKLVMGTLKLQILGEVHFVEKPHSLLQISGGSTTLK KGPNPWSFPSPCALFPT (SEQ ID NO: 36), and

[121] The leader sequence of the B7-H9 protein: MALMLSLVLSLLKLGSG (SEQ ID NO: 37). Polynucleotides encoding these polypeptides are also encompassed by the invention, as are antibodies that bind one or more of these polypeptides. Moreover, fragments and variants of these polypeptides (e.g., fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof) are encompassed by the invention. Antibodies that bind these fragments and variants of the invention are also encompassed by the invention. Polynucleotides encoding these fragments and variants are also encompassed by the invention.

[122] Also preferred are polypeptides comprising, or alternatively consisting of, fragments of the B7-H9 protein demonstrating functional activity (SEQ ID NO: 16). Polynucleotides encoding these polypeptides are also encompassed by the invention. By functional activity is meant, a polypeptide fragment capable of displaying one or more known functional activities associated with the full-length (complete) B7-H9 protein. Such functional activities include, but are not limited to, biological activity (e.g., T cell costimulatory activity, ability to bind ICOS, CD28 or CTLA4, and ability to induce or inhibit cytokine production), antigenicity [ability to bind (or compete with a B7-H9 polypeptide for binding) to an anti-B7-H9 antibody], immunogenicity (ability to generate antibody which binds to a B7-H9 polypeptide), ability to form multimers with B7-H9 polypeptides of the invention, and ability to bind to a receptor for a B7-H9 polypeptide.

[123] Figures 5A-C show the nucleotide (SEQ ID NO: 4) and deduced amino acid sequence (SEQ ID NO: 16) corresponding to this gene.

[124] Figure 6 shows an analysis of the amino acid sequence (SEQ ID NO: 16). Alpha, beta, turn and coil regions; hydrophilicity and hydrophobicity; amphipathic regions; flexible regions; antigenic index and surface probability are shown, and all were generated using the default settings of the recited computer algorithyms. In the "Antigenic Index or Jameson-Wolf" graph, the positive peaks indicate locations of the highly antigenic regions of the protein, i.e., regions from which epitope-bearing peptides of the invention can be obtained. Polypeptides comprising, or alternatively consisting of, domains defined by these graphs are

contemplated by the present invention, as are polynucleotides encoding these polypeptides. The data presented in Figure 6 are also represented in tabular form in Table 5. The columns are labeled with the headings "Res", "Position", and Roman Numerals I-XIV. The column headings refer to the following features of the amino acid sequence presented in Figure 6, and Table 5: "Res": amino acid residue of SEQ ID NO: 16 and Figures 5A-C; "Position": position of the corresponding residue within SEQ ID NO: 16 and Figures 5A-C; I: Alpha, Regions - Garnier-Robson; II: Alpha, Regions - Chou-Fasman; III: Beta, Regions - Garnier-Robson; IV: Beta, Regions - Chou-Fasman; V: Turn, Regions - Garnier-Robson; VI: Turn, Regions - Chou-Fasman; VII: Coil, Regions - Garnier-Robson; VIII: Hydrophilicity Plot - Kyte-Doolittle; IX: Hydrophobicity Plot - Hopp-Woods; X: Alpha, Amphipathic Regions - Eisenberg; XI: Beta, Amphipathic Regions - Eisenberg; XII: Flexible Regions - Karplus-Schulz; XIII: Antigenic Index - Jameson-Wolf; and XIV: Surface Probability Plot - Emini. Preferred embodiments of the invention in this regard include fragments that comprise, or alternatively consisting of, one or more of the following regions: alpha-helix and alpha-helix forming regions ("alpha-regions"), beta-sheet and beta-sheet forming regions ("beta-regions"), turn and turn-forming regions ("turn-regions"), coil and coil-forming regions ("coil-regions"), hydrophilic regions, hydrophobic regions, alpha amphipathic regions, beta amphipathic regions, flexible regions, surface-forming regions and high antigenic index regions. The data representing the structural or functional attributes of the protein set forth in Figure 6 and/or Table 5, as described above, was generated using the various modules and algorithms of the DNA*STAR set on default parameters. In a preferred embodiment, the data presented in columns VIII, IX, XIII, and XIV of Table 5 can be used to determine regions of the protein which exhibit a high degree of potential for antigenicity. Regions of high antigenicity are determined from the data presented in columns VIII, IX, XIII, and/or XIV by choosing values which represent regions of the polypeptide which are likely to be exposed on the surface of the polypeptide in an environment in which antigen recognition may occur in the process of initiation of an immune response. Certain preferred regions in these regards are set out in Figure 6, but may, as shown in Table 5, be represented or identified by using tabular representations of the data presented in Figure 6. The DNA*STAR computer algorithm used to generate Figure 6 (set on the original default parameters) was used to present the data in Figure 6 in a tabular format (See Table 5). The tabular format of the data

in Figure 6 (See Table 5) is used to easily determine specific boundaries of a preferred region.

[125] The present invention is further directed to fragments of the polynucleotide sequences described herein. By a fragment of, for example, the polynucleotide sequence of a deposited cDNA or the nucleotide sequence shown in SEQ ID NO: 4, is intended polynucleotide fragments at least about 15nt, and more preferably at least about 20 nt, at least about 25nt, still more preferably at least about 30 nt, at least about 35nt, and even more preferably, at least about 40 nt in length, at least about 45nt in length, at least about 50nt in length, at least about 60nt in length, at least about 70nt in length, at least about 80nt in length, at least about 90nt in length, at least about 100nt in length, at least about 125nt in length, at least about 150nt in length, at least about 175nt in length, which are useful as diagnostic probes and primers as discussed herein. Of course, larger fragments 200-1500 nt in length are also useful according to the present invention, as are fragments corresponding to most, if not all, of the nucleotide sequence of a deposited cDNA or as shown in SEQ ID NO: 4. By a fragment at least 20 nt in length, for example, is intended fragments which include 20 or more contiguous bases from the nucleotide sequence of a deposited cDNA or the nucleotide sequence as shown in SEQ ID NO: 4. In this context "about" includes the particularly recited size, an sizes larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Representative examples of polynucleotide fragments of the invention include, for example, fragments that comprise, or alternatively, consist of, a sequence from about nucleotide 1 to about 50, from about 51 to about 100, from about 101 to about 150, from about 151 to about 200, from about 201 to about 250, from about 251 to about 300, from about 301 to about 350, from about 351 to about 400, from about 401 to about 450, from about 451 to about 500, and from about 501 to about 550, and from about 551 to about 600, from about 601 to about 650, from about 651 to about 700, from about 701 to about 750, from about 751 to about 800, and from about 801 to about 860, of SEQ ID NO: 4, or the complementary strand thereto, or the cDNA contained in a deposited clone. In this context "about" includes the particularly recited ranges, and ranges larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. In additional embodiments, the polynucleotides of the invention encode functional attributes of the corresponding protein.

[126] Preferred polypeptide fragments of the invention comprise, or alternatively consist of, the secreted protein having a continuous series of deleted residues from the amino or the

carboxy terminus, or both. Particularly, N-terminal deletions of the polypeptide can be described by the general formula m-318 where m is an integer from 2 to 313, where m corresponds to the position of the amino acid residue identified in SEQ ID NO: 16. More in particular, the invention provides polynucleotides encoding polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group: A-2 to T-318; L-3 to T-318; M-4 to T-318; L-5 to T-318; S-6 to T-318; L-7 to T-318; V-8 to T-318; L-9 to T-318; S-10 to T-318; L-11 to T-318; L-12 to T-318; K-13 to T-318; L-14 to T-318; G-15 to T-318; S-16 to T-318; G-17 to T-318; Q-18 to T-318; W-19 to T-318; Q-20 to T-318; V-21 to T-318; F-22 to T-318; G-23 to T-318; P-24 to T-318; D-25 to T-318; K-26 to T-318; P-27 to T-318; V-28 to T-318; Q-29 to T-318; A-30 to T-318; L-31 to T-318; V-32 to T-318; G-33 to T-318; E-34 to T-318; D-35 to T-318; A-36 to T-318; A-37 to T-318; F-38 to T-318; S-39 to T-318; C-40 to T-318; F-41 to T-318; L-42 to T-318; S-43 to T-318; P-44 to T-318; K-45 to T-318; T-46 to T-318; N-47 to T-318; A-48 to T-318; E-49 to T-318; A-50 to T-318; M-51 to T-318; E-52 to T-318; V-53 to T-318; R-54 to T-318; F-55 to T-318; F-56 to T-318; R-57 to T-318; G-58 to T-318; Q-59 to T-318; F-60 to T-318; S-61 to T-318; S-62 to T-318; V-63 to T-318; V-64 to T-318; H-65 to T-318; L-66 to T-318; Y-67 to T-318; R-68 to T-318; D-69 to T-318; G-70 to T-318; K-71 to T-318; D-72 to T-318; Q-73 to T-318; P-74 to T-318; F-75 to T-318; M-76 to T-318; Q-77 to T-318; M-78 to T-318; P-79 to T-318; Q-80 to T-318; Y-81 to T-318; Q-82 to T-318; G-83 to T-318; R-84 to T-318; T-85 to T-318; K-86 to T-318; L-87 to T-318; V-88 to T-318; K-89 to T-318; D-90 to T-318; S-91 to T-318; I-92 to T-318; A-93 to T-318; E-94 to T-318; G-95 to T-318; R-96 to T-318; I-97 to T-318; S-98 to T-318; L-99 to T-318; R-100 to T-318; L-101 to T-318; E-102 to T-318; N-103 to T-318; I-104 to T-318; T-105 to T-318; V-106 to T-318; L-107 to T-318; D-108 to T-318; A-109 to T-318; G-110 to T-318; L-111 to T-318; Y-112 to T-318; G-113 to T-318; C-114 to T-318; R-115 to T-318; I-116 to T-318; S-117 to T-318; S-118 to T-318; Q-119 to T-318; S-120 to T-318; Y-121 to T-318; Y-122 to T-318; Q-123 to T-318; K-124 to T-318; A-125 to T-318; I-126 to T-318; W-127 to T-318; E-128 to T-318; L-129 to T-318; Q-130 to T-318; V-131 to T-318; S-132 to T-318; A-133 to T-318; L-134 to T-318; G-135 to T-318; S-136 to T-318; V-137 to T-318; P-138 to T-318; L-139 to T-318; I-140 to T-318; S-141 to T-318; I-142 to T-318; A-143 to T-318; G-144 to T-318; Y-145 to T-318; V-146 to T-318; D-147 to T-318; R-148 to T-318; D-149 to T-318; I-150 to T-318; Q-151 to T-318; L-152 to T-318; L-153 to T-318; C-154 to T-318; Q-155 to T-318; S-156 to T-318; S-157 to T-318; G-158 to T-318; W-159 to T-318; F-

160 to T-318; P-161 to T-318; R-162 to T-318; P-163 to T-318; T-164 to T-318; A-165 to T-318; K-166 to T-318; W-167 to T-318; K-168 to T-318; G-169 to T-318; P-170 to T-318; Q-171 to T-318; G-172 to T-318; Q-173 to T-318; D-174 to T-318; L-175 to T-318; S-176 to T-318; T-177 to T-318; D-178 to T-318; S-179 to T-318; R-180 to T-318; T-181 to T-318; N-182 to T-318; R-183 to T-318; D-184 to T-318; M-185 to T-318; H-186 to T-318; G-187 to T-318; L-188 to T-318; F-189 to T-318; D-190 to T-318; V-191 to T-318; E-192 to T-318; I-193 to T-318; S-194 to T-318; L-195 to T-318; T-196 to T-318; V-197 to T-318; Q-198 to T-318; E-199 to T-318; N-200 to T-318; A-201 to T-318; G-202 to T-318; S-203 to T-318; I-204 to T-318; S-205 to T-318; C-206 to T-318; S-207 to T-318; M-208 to T-318; R-209 to T-318; H-210 to T-318; A-211 to T-318; H-212 to T-318; L-213 to T-318; S-214 to T-318; R-215 to T-318; E-216 to T-318; V-217 to T-318; E-218 to T-318; S-219 to T-318; R-220 to T-318; V-221 to T-318; Q-222 to T-318; I-223 to T-318; G-224 to T-318; D-225 to T-318; W-226 to T-318; R-227 to T-318; R-228 to T-318; K-229 to T-318; H-230 to T-318; G-231 to T-318; Q-232 to T-318; A-233 to T-318; G-234 to T-318; K-235 to T-318; R-236 to T-318; K-237 to T-318; Y-238 to T-318; S-239 to T-318; S-240 to T-318; S-241 to T-318; H-242 to T-318; I-243 to T-318; Y-244 to T-318; D-245 to T-318; S-246 to T-318; F-247 to T-318; P-248 to T-318; S-249 to T-318; L-250 to T-318; S-251 to T-318; F-252 to T-318; M-253 to T-318; D-254 to T-318; F-255 to T-318; Y-256 to T-318; I-257 to T-318; L-258 to T-318; R-259 to T-318; P-260 to T-318; V-261 to T-318; G-262 to T-318; P-263 to T-318; C-264 to T-318; R-265 to T-318; A-266 to T-318; K-267 to T-318; L-268 to T-318; V-269 to T-318; M-270 to T-318; G-271 to T-318; T-272 to T-318; L-273 to T-318; K-274 to T-318; L-275 to T-318; Q-276 to T-318; I-277 to T-318; L-278 to T-318; G-279 to T-318; E-280 to T-318; V-281 to T-318; H-282 to T-318; F-283 to T-318; V-284 to T-318; E-285 to T-318; K-286 to T-318; P-287 to T-318; H-288 to T-318; S-289 to T-318; L-290 to T-318; L-291 to T-318; Q-292 to T-318; I-293 to T-318; S-294 to T-318; G-295 to T-318; G-296 to T-318; S-297 to T-318; T-298 to T-318; T-299 to T-318; L-300 to T-318; K-301 to T-318; K-302 to T-318; G-303 to T-318; P-304 to T-318; N-305 to T-318; P-306 to T-318; W-307 to T-318; S-308 to T-318; F-309 to T-318; P-310 to T-318; S-311 to T-318; P-312 to T-318; and C-313 to T-318 of SEQ ID NO: 16. Polynucleotides encoding these polypeptides are also encompassed by the invention, as are antibodies that bind one or more of these polypeptides. Moreover, fragments and variants of these polypeptides (e.g., fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and

polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof) are encompassed by the invention. Antibodies that bind these fragments and variants of the invention are also encompassed by the invention. Polynucleotides encoding these fragments and variants are also encompassed by the invention.

[127] Accordingly, the present invention further provides polypeptides having one or more residues deleted from the carboxy terminus of the amino acid sequence of the polypeptide shown in Figures 5A-C (SEQ ID NO: 16), as described by the general formula 1-n, where n is an integer from 7 to 317, where n corresponds to the position of the amino acid residue identified in SEQ ID NO: 16. Additionally, the invention provides polynucleotides encoding polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the following group of C-terminal deletions: M-1 to P-317; M-1 to F-316; M-1 to L-315; M-1 to A-314; M-1 to C-313; M-1 to P-312; M-1 to S-311; M-1 to P-310; M-1 to F-309; M-1 to S-308; M-1 to W-307; M-1 to P-306; M-1 to N-305; M-1 to P-304; M-1 to G-303; M-1 to K-302; M-1 to K-301; M-1 to L-300; M-1 to T-299; M-1 to T-298; M-1 to S-297; M-1 to G-296; M-1 to G-295; M-1 to S-294; M-1 to I-293; M-1 to Q-292; M-1 to L-291; M-1 to L-290; M-1 to S-289; M-1 to H-288; M-1 to P-287; M-1 to K-286; M-1 to E-285; M-1 to V-284; M-1 to F-283; M-1 to H-282; M-1 to V-281; M-1 to E-280; M-1 to G-279; M-1 to L-278; M-1 to I-277; M-1 to Q-276; M-1 to L-275; M-1 to K-274; M-1 to L-273; M-1 to T-272; M-1 to G-271; M-1 to M-270; M-1 to V-269; M-1 to L-268; M-1 to K-267; M-1 to A-266; M-1 to R-265; M-1 to C-264; M-1 to P-263; M-1 to G-262; M-1 to V-261; M-1 to P-260; M-1 to R-259; M-1 to L-258; M-1 to I-257; M-1 to Y-256; M-1 to F-255; M-1 to D-254; M-1 to M-253; M-1 to F-252; M-1 to S-251; M-1 to L-250; M-1 to S-249; M-1 to P-248; M-1 to F-247; M-1 to S-246; M-1 to D-245; M-1 to Y-244; M-1 to I-243; M-1 to H-242; M-1 to S-241; M-1 to S-240; M-1 to S-239; M-1 to Y-238; M-1 to K-237; M-1 to R-236; M-1 to K-235; M-1 to G-234; M-1 to A-233; M-1 to Q-232; M-1 to G-231; M-1 to H-230; M-1 to K-229; M-1 to R-228; M-1 to R-227; M-1 to W-226; M-1 to D-225; M-1 to G-224; M-1 to I-223; M-1 to Q-222; M-1 to V-221; M-1 to R-220; M-1 to S-219; M-1 to E-218; M-1 to V-217; M-1 to E-216; M-1 to R-215; M-1 to S-214; M-1 to L-213; M-1 to H-212; M-1 to A-211; M-1 to H-210; M-1 to R-209; M-1 to M-208; M-1 to S-207; M-1 to C-206; M-1 to S-205; M-1 to I-204; M-1 to S-203; M-1 to G-202; M-1 to A-201; M-1 to N-200; M-1 to E-199; M-1 to Q-198; M-1 to V-197; M-1 to T-196; M-1 to L-195; M-1 to S-194; M-1 to I-193; M-1

to E-192; M-1 to V-191; M-1 to D-190; M-1 to F-189; M-1 to L-188; M-1 to G-187; M-1 to H-186; M-1 to M-185; M-1 to D-184; M-1 to R-183; M-1 to N-182; M-1 to T-181; M-1 to R-180; M-1 to S-179; M-1 to D-178; M-1 to T-177; M-1 to S-176; M-1 to L-175; M-1 to D-174; M-1 to Q-173; M-1 to G-172; M-1 to Q-171; M-1 to P-170; M-1 to G-169; M-1 to K-168; M-1 to W-167; M-1 to K-166; M-1 to A-165; M-1 to T-164; M-1 to P-163; M-1 to R-162; M-1 to P-161; M-1 to F-160; M-1 to W-159; M-1 to G-158; M-1 to S-157; M-1 to S-156; M-1 to Q-155; M-1 to C-154; M-1 to L-153; M-1 to L-152; M-1 to Q-151; M-1 to I-150; M-1 to D-149; M-1 to R-148; M-1 to D-147; M-1 to V-146; M-1 to Y-145; M-1 to G-144; M-1 to A-143; M-1 to I-142; M-1 to S-141; M-1 to I-140; M-1 to L-139; M-1 to P-138; M-1 to V-137; M-1 to S-136; M-1 to G-135; M-1 to L-134; M-1 to A-133; M-1 to S-132; M-1 to V-131; M-1 to Q-130; M-1 to L-129; M-1 to E-128; M-1 to W-127; M-1 to I-126; M-1 to A-125; M-1 to K-124; M-1 to Q-123; M-1 to Y-122; M-1 to Y-121; M-1 to S-120; M-1 to Q-119; M-1 to S-118; M-1 to S-117; M-1 to I-116; M-1 to R-115; M-1 to C-114; M-1 to G-113; M-1 to Y-112; M-1 to L-111; M-1 to G-110; M-1 to A-109; M-1 to D-108; M-1 to L-107; M-1 to V-106; M-1 to T-105; M-1 to I-104; M-1 to N-103; M-1 to E-102; M-1 to L-101; M-1 to R-100; M-1 to L-99; M-1 to S-98; M-1 to I-97; M-1 to R-96; M-1 to G-95; M-1 to E-94; M-1 to A-93; M-1 to I-92; M-1 to S-91; M-1 to D-90; M-1 to K-89; M-1 to V-88; M-1 to L-87; M-1 to K-86; M-1 to T-85; M-1 to R-84; M-1 to G-83; M-1 to Q-82; M-1 to Y-81; M-1 to Q-80; M-1 to P-79; M-1 to M-78; M-1 to Q-77; M-1 to M-76; M-1 to F-75; M-1 to P-74; M-1 to Q-73; M-1 to D-72; M-1 to K-71; M-1 to G-70; M-1 to D-69; M-1 to R-68; M-1 to Y-67; M-1 to L-66; M-1 to H-65; M-1 to V-64; M-1 to V-63; M-1 to S-62; M-1 to S-61; M-1 to F-60; M-1 to Q-59; M-1 to G-58; M-1 to R-57; M-1 to F-56; M-1 to F-55; M-1 to R-54; M-1 to V-53; M-1 to E-52; M-1 to M-51; M-1 to A-50; M-1 to E-49; M-1 to A-48; M-1 to N-47; M-1 to T-46; M-1 to K-45; M-1 to P-44; M-1 to S-43; M-1 to L-42; M-1 to F-41; M-1 to C-40; M-1 to S-39; M-1 to F-38; M-1 to A-37; M-1 to A-36; M-1 to D-35; M-1 to E-34; M-1 to G-33; M-1 to V-32; M-1 to L-31; M-1 to A-30; M-1 to Q-29; M-1 to V-28; M-1 to P-27; M-1 to K-26; M-1 to D-25; M-1 to P-24; M-1 to G-23; M-1 to F-22; M-1 to V-21; M-1 to Q-20; M-1 to W-19; M-1 to Q-18; M-1 to G-17; M-1 to S-16; M-1 to G-15; M-1 to L-14; M-1 to K-13; M-1 to L-12; M-1 to L-11; M-1 to S-10; M-1 to L-9; M-1 to V-8; and M-1 to L-7 of SEQ ID NO: 16. Polynucleotides encoding these polypeptides are also encompassed by the invention, as are antibodies that bind one or more of these polypeptides. Moreover, fragments and variants of these polypeptides (e.g., fragments as described herein, polypeptides at least 80%,

85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof) are encompassed by the invention. Antibodies that bind these fragments and variants of the invention are also encompassed by the invention. Polynucleotides encoding these fragments and variants are also encompassed by the invention.

[128] Also as mentioned above, even if deletion of one or more amino acids from the C-terminus of a protein results in modification of loss of one or more biological functions of the protein (e.g., ability to inhibit the Mixed Lymphocyte Reaction), other functional activities (e.g., biological activities, ability to multimerize, ability to bind receptor, ability to generate antibodies, ability to bind antibodies) may still be retained. For example, the ability of the shortened polypeptide to induce and/or bind to antibodies which recognize the complete or mature forms of the polypeptide generally will be retained when less than the majority of the residues of the complete or mature polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a polypeptide with a large number of deleted C-terminal amino acid residues may retain some biological or immunogenic activities. In fact, peptides composed of as few as six amino acid residues may often evoke an immune response.

[129] More in particular, the invention provides polynucleotides encoding polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group of N-terminal deletions of the mature portion of the B7-H9 protein (SEQ ID NO: 36): W-19 to T-318; Q-20 to T-318; V-21 to T-318; F-22 to T-318; G-23 to T-318; P-24 to T-318; D-25 to T-318; K-26 to T-318; P-27 to T-318; V-28 to T-318; Q-29 to T-318; A-30 to T-318; L-31 to T-318; V-32 to T-318; G-33 to T-318; E-34 to T-318; D-35 to T-318; A-36 to T-318; A-37 to T-318; F-38 to T-318; S-39 to T-318; C-40 to T-318; F-41 to T-318; L-42 to T-318; S-43 to T-318; P-44 to T-318; K-45 to T-318; T-46 to T-318; N-47 to T-318; A-48 to T-318; E-49 to T-318; A-50 to T-318; M-51 to T-318; E-52 to T-318; V-53 to T-318; R-54 to T-318; F-55 to T-318; F-56 to T-318; R-57 to T-318; G-58 to T-318; Q-59 to T-318; F-60 to T-318; S-61 to T-318; S-62 to T-318; V-63 to T-318; V-64 to T-318; H-65 to T-318; L-66 to T-318; Y-67 to T-318; R-68 to T-318; D-69 to T-318; G-70 to T-318; K-71 to T-318; D-72 to T-318; Q-73 to

T-318; P-74 to T-318; F-75 to T-318; M-76 to T-318; Q-77 to T-318; M-78 to T-318; P-79 to T-318; Q-80 to T-318; Y-81 to T-318; Q-82 to T-318; G-83 to T-318; R-84 to T-318; T-85 to T-318; K-86 to T-318; L-87 to T-318; V-88 to T-318; K-89 to T-318; D-90 to T-318; S-91 to T-318; I-92 to T-318; A-93 to T-318; E-94 to T-318; G-95 to T-318; R-96 to T-318; I-97 to T-318; S-98 to T-318; L-99 to T-318; R-100 to T-318; L-101 to T-318; E-102 to T-318; N-103 to T-318; I-104 to T-318; T-105 to T-318; V-106 to T-318; L-107 to T-318; D-108 to T-318; A-109 to T-318; G-110 to T-318; L-111 to T-318; Y-112 to T-318; G-113 to T-318; C-114 to T-318; R-115 to T-318; I-116 to T-318; S-117 to T-318; S-118 to T-318; Q-119 to T-318; S-120 to T-318; Y-121 to T-318; Y-122 to T-318; Q-123 to T-318; K-124 to T-318; A-125 to T-318; I-126 to T-318; W-127 to T-318; E-128 to T-318; L-129 to T-318; Q-130 to T-318; V-131 to T-318; S-132 to T-318; A-133 to T-318; L-134 to T-318; G-135 to T-318; S-136 to T-318; V-137 to T-318; P-138 to T-318; L-139 to T-318; I-140 to T-318; S-141 to T-318; I-142 to T-318; A-143 to T-318; G-144 to T-318; Y-145 to T-318; V-146 to T-318; D-147 to T-318; R-148 to T-318; D-149 to T-318; I-150 to T-318; Q-151 to T-318; L-152 to T-318; L-153 to T-318; C-154 to T-318; Q-155 to T-318; S-156 to T-318; S-157 to T-318; G-158 to T-318; W-159 to T-318; F-160 to T-318; P-161 to T-318; R-162 to T-318; P-163 to T-318; T-164 to T-318; A-165 to T-318; K-166 to T-318; W-167 to T-318; K-168 to T-318; G-169 to T-318; P-170 to T-318; Q-171 to T-318; G-172 to T-318; Q-173 to T-318; D-174 to T-318; L-175 to T-318; S-176 to T-318; T-177 to T-318; D-178 to T-318; S-179 to T-318; R-180 to T-318; T-181 to T-318; N-182 to T-318; R-183 to T-318; D-184 to T-318; M-185 to T-318; H-186 to T-318; G-187 to T-318; L-188 to T-318; F-189 to T-318; D-190 to T-318; V-191 to T-318; E-192 to T-318; I-193 to T-318; S-194 to T-318; L-195 to T-318; T-196 to T-318; V-197 to T-318; Q-198 to T-318; E-199 to T-318; N-200 to T-318; A-201 to T-318; G-202 to T-318; S-203 to T-318; I-204 to T-318; S-205 to T-318; C-206 to T-318; S-207 to T-318; M-208 to T-318; R-209 to T-318; H-210 to T-318; A-211 to T-318; H-212 to T-318; L-213 to T-318; S-214 to T-318; R-215 to T-318; E-216 to T-318; V-217 to T-318; E-218 to T-318; S-219 to T-318; R-220 to T-318; V-221 to T-318; Q-222 to T-318; I-223 to T-318; G-224 to T-318; D-225 to T-318; W-226 to T-318; R-227 to T-318; R-228 to T-318; K-229 to T-318; H-230 to T-318; G-231 to T-318; Q-232 to T-318; A-233 to T-318; G-234 to T-318; K-235 to T-318; R-236 to T-318; K-237 to T-318; Y-238 to T-318; S-239 to T-318; S-240 to T-318; S-241 to T-318; H-242 to T-318; I-243 to T-318; Y-244 to T-318; D-245 to T-318; S-246 to T-318; F-247 to T-318; P-248 to T-318; S-249 to T-318; L-250 to T-318; S-251 to T-

318; F-252 to T-318; M-253 to T-318; D-254 to T-318; F-255 to T-318; Y-256 to T-318; I-257 to T-318; L-258 to T-318; R-259 to T-318; P-260 to T-318; V-261 to T-318; G-262 to T-318; P-263 to T-318; C-264 to T-318; R-265 to T-318; A-266 to T-318; K-267 to T-318; L-268 to T-318; V-269 to T-318; M-270 to T-318; G-271 to T-318; T-272 to T-318; L-273 to T-318; K-274 to T-318; L-275 to T-318; Q-276 to T-318; I-277 to T-318; L-278 to T-318; G-279 to T-318; E-280 to T-318; V-281 to T-318; H-282 to T-318; F-283 to T-318; V-284 to T-318; E-285 to T-318; K-286 to T-318; P-287 to T-318; H-288 to T-318; S-289 to T-318; L-290 to T-318; L-291 to T-318; Q-292 to T-318; I-293 to T-318; S-294 to T-318; G-295 to T-318; G-296 to T-318; S-297 to T-318; T-298 to T-318; T-299 to T-318; L-300 to T-318; K-301 to T-318; K-302 to T-318; G-303 to T-318; P-304 to T-318; N-305 to T-318; P-306 to T-318; W-307 to T-318; S-308 to T-318; F-309 to T-318; P-310 to T-318; S-311 to T-318; P-312 to T-318; and/or C-313 to T-318 of SEQ ID NO: 16. Polynucleotides encoding these polypeptides are also encompassed by the invention, as are antibodies that bind one or more of these polypeptides. Moreover, fragments and variants of these polypeptides (e.g., fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof) are encompassed by the invention. Antibodies that bind these fragments and variants of the invention are also encompassed by the invention. Polynucleotides encoding these fragments and variants are also encompassed by the invention.

[130] Additionally, the invention provides polynucleotides encoding polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group of C-terminal deletions of the mature portion of the B7-H9 protein (SEQ ID NO: 36): Q-18 to P-317; Q-18 to F-316; Q-18 to L-315; Q-18 to A-314; Q-18 to C-313; Q-18 to P-312; Q-18 to S-311; Q-18 to P-310; Q-18 to F-309; Q-18 to S-308; Q-18 to W-307; Q-18 to P-306; Q-18 to N-305; Q-18 to P-304; Q-18 to G-303; Q-18 to K-302; Q-18 to K-301; Q-18 to L-300; Q-18 to T-299; Q-18 to T-298; Q-18 to S-297; Q-18 to G-296; Q-18 to G-295; Q-18 to S-294; Q-18 to I-293; Q-18 to Q-292; Q-18 to L-291; Q-18 to L-290; Q-18 to S-289; Q-18 to H-288; Q-18 to P-287; Q-18 to K-286; Q-18 to E-285; Q-18 to V-284; Q-18 to F-283; Q-18 to H-282; Q-18 to V-281; Q-18 to E-280; Q-18 to G-279; Q-18 to L-278; Q-18 to I-277; Q-18 to Q-276; Q-18 to L-275; Q-18 to K-274; Q-18 to L-273; Q-18 to T-272; Q-18 to G-271; Q-18

to M-270; Q-18 to V-269; Q-18 to L-268; Q-18 to K-267; Q-18 to A-266; Q-18 to R-265; Q-18 to C-264; Q-18 to P-263; Q-18 to G-262; Q-18 to V-261; Q-18 to P-260; Q-18 to R-259; Q-18 to L-258; Q-18 to I-257; Q-18 to Y-256; Q-18 to F-255; Q-18 to D-254; Q-18 to M-253; Q-18 to F-252; Q-18 to S-251; Q-18 to L-250; Q-18 to S-249; Q-18 to P-248; Q-18 to F-247; Q-18 to S-246; Q-18 to D-245; Q-18 to Y-244; Q-18 to I-243; Q-18 to H-242; Q-18 to S-241; Q-18 to S-240; Q-18 to S-239; Q-18 to Y-238; Q-18 to K-237; Q-18 to R-236; Q-18 to K-235; Q-18 to G-234; Q-18 to A-233; Q-18 to Q-232; Q-18 to G-231; Q-18 to H-230; Q-18 to K-229; Q-18 to R-228; Q-18 to R-227; Q-18 to W-226; Q-18 to D-225; Q-18 to G-224; Q-18 to I-223; Q-18 to Q-222; Q-18 to V-221; Q-18 to R-220; Q-18 to S-219; Q-18 to E-218; Q-18 to V-217; Q-18 to E-216; Q-18 to R-215; Q-18 to S-214; Q-18 to L-213; Q-18 to H-212; Q-18 to A-211; Q-18 to H-210; Q-18 to R-209; Q-18 to M-208; Q-18 to S-207; Q-18 to C-206; Q-18 to S-205; Q-18 to I-204; Q-18 to S-203; Q-18 to G-202; Q-18 to A-201; Q-18 to N-200; Q-18 to E-199; Q-18 to Q-198; Q-18 to V-197; Q-18 to T-196; Q-18 to L-195; Q-18 to S-194; Q-18 to I-193; Q-18 to E-192; Q-18 to V-191; Q-18 to D-190; Q-18 to F-189; Q-18 to L-188; Q-18 to G-187; Q-18 to H-186; Q-18 to M-185; Q-18 to D-184; Q-18 to R-183; Q-18 to N-182; Q-18 to T-181; Q-18 to R-180; Q-18 to S-179; Q-18 to D-178; Q-18 to T-177; Q-18 to S-176; Q-18 to L-175; Q-18 to D-174; Q-18 to Q-173; Q-18 to G-172; Q-18 to Q-171; Q-18 to P-170; Q-18 to G-169; Q-18 to K-168; Q-18 to W-167; Q-18 to K-166; Q-18 to A-165; Q-18 to T-164; Q-18 to P-163; Q-18 to R-162; Q-18 to P-161; Q-18 to F-160; Q-18 to W-159; Q-18 to G-158; Q-18 to S-157; Q-18 to S-156; Q-18 to Q-155; Q-18 to C-154; Q-18 to L-153; Q-18 to L-152; Q-18 to Q-151; Q-18 to I-150; Q-18 to D-149; Q-18 to R-148; Q-18 to D-147; Q-18 to V-146; Q-18 to Y-145; Q-18 to G-144; Q-18 to A-143; Q-18 to I-142; Q-18 to S-141; Q-18 to I-140; Q-18 to L-139; Q-18 to P-138; Q-18 to V-137; Q-18 to S-136; Q-18 to G-135; Q-18 to L-134; Q-18 to A-133; Q-18 to S-132; Q-18 to V-131; Q-18 to Q-130; Q-18 to L-129; Q-18 to E-128; Q-18 to W-127; Q-18 to I-126; Q-18 to A-125; Q-18 to K-124; Q-18 to Q-123; Q-18 to Y-122; Q-18 to Y-121; Q-18 to S-120; Q-18 to Q-119; Q-18 to S-118; Q-18 to S-117; Q-18 to I-116; Q-18 to R-115; Q-18 to C-114; Q-18 to G-113; Q-18 to Y-112; Q-18 to L-111; Q-18 to G-110; Q-18 to A-109; Q-18 to D-108; Q-18 to L-107; Q-18 to V-106; Q-18 to T-105; Q-18 to I-104; Q-18 to N-103; Q-18 to E-102; Q-18 to L-101; Q-18 to R-100; Q-18 to L-99; Q-18 to S-98; Q-18 to I-97; Q-18 to R-96; Q-18 to G-95; Q-18 to E-94; Q-18 to A-93; Q-18 to I-92; Q-18 to S-91; Q-18 to D-90; Q-18 to K-89; Q-18 to V-88; Q-18 to L-87; Q-18 to K-86; Q-18 to T-85; Q-18 to R-84; Q-18 to G-83; Q-18 to Q-82; Q-18 to

Y-81; Q-18 to Q-80; Q-18 to P-79; Q-18 to M-78; Q-18 to Q-77; Q-18 to M-76; Q-18 to F-75; Q-18 to P-74; Q-18 to Q-73; Q-18 to D-72; Q-18 to K-71; Q-18 to G-70; Q-18 to D-69; Q-18 to R-68; Q-18 to Y-67; Q-18 to L-66; Q-18 to H-65; Q-18 to V-64; Q-18 to V-63; Q-18 to S-62; Q-18 to S-61; Q-18 to F-60; Q-18 to Q-59; Q-18 to G-58; Q-18 to R-57; Q-18 to F-56; Q-18 to F-55; Q-18 to R-54; Q-18 to V-53; Q-18 to E-52; Q-18 to M-51; Q-18 to A-50; Q-18 to E-49; Q-18 to A-48; Q-18 to N-47; Q-18 to T-46; Q-18 to K-45; Q-18 to P-44; Q-18 to S-43; Q-18 to L-42; Q-18 to F-41; Q-18 to C-40; Q-18 to S-39; Q-18 to F-38; Q-18 to A-37; Q-18 to A-36; Q-18 to D-35; Q-18 to E-34; Q-18 to G-33; Q-18 to V-32; Q-18 to L-31; Q-18 to A-30; Q-18 to Q-29; Q-18 to V-28; Q-18 to P-27; Q-18 to K-26; Q-18 to D-25; and/or Q-18 to P-24 of SEQ ID NO: 16. Polynucleotides encoding these polypeptides are also encompassed by the invention, as are antibodies that bind one or more of these polypeptides. Moreover, fragments and variants of these polypeptides (e.g., fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof) are encompassed by the invention. Antibodies that bind these fragments and variants of the invention are also encompassed by the invention. Polynucleotides encoding these fragments and variants are also encompassed by the invention.

[131] In addition, any of the above listed N- or C-terminal deletions can be combined to produce a N- and C-terminal deleted polypeptide. The invention also provides polypeptides comprising, or alternatively consisting of, one or more amino acids deleted from both the amino and the carboxyl termini, which may be described generally as having residues m-n of SEQ ID NO: 16, where n and m are integers as described above. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[132] The present invention is also directed to proteins containing polypeptides at least 80%, 85%, 90%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to a polypeptide sequence set forth herein as m-n. In preferred embodiments, the application is directed to proteins containing polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to polypeptides having the amino acid sequence of the specific N- and C-terminal deletions recited herein. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[133] Also included are polynucleotide sequences encoding a polypeptide consisting of a portion of the complete amino acid sequence encoded by a cDNA clone contained in ATCC Deposit No. PTA-2332, where this portion excludes any integer of amino acid residues from 1 to about 312 amino acids from the amino terminus of the complete amino acid sequence encoded by a cDNA clone contained in ATCC Deposit No. PTA-2332, or any integer of amino acid residues from 1 to about 312 amino acids from the carboxy terminus, or any combination of the above amino terminal and carboxy terminal deletions, of the complete amino acid sequence encoded by the cDNA clone contained in ATCC Deposit No. PTA-2332. Polypeptides encoded by these polynucleotides also are encompassed by the invention.

[134] As described herein or otherwise known in the art, the polynucleotides of the invention have uses that include, but are not limited to, serving as probes or primers in chromosome identification, chromosome mapping, and linkage analysis.

[135] It has been discovered that this gene is expressed in small intestine, colon, and colon tumor tissues.

[136] Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of gastrointestinal system tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases and/or disorders involving immune system activation, stimulation and/or surveillance, particularly involving T cells and/or neutrophils, as well as diseases and/or disorders of the gastrointestinal system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). Particularly contemplated are the use of antibodies directed against the extracellular portion of this protein which act as antagonists for the activity of the B7-H9 protein. Such antagonistic antibodies would be useful for the prevention and/or inhibition of such biological activites as are disclosed herein (e.g. T cell modulated activities).

[137] For a number of disorders of the above tissues or cells, particularly of the gastrointestinal and immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, gastrointestinal, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an

individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

[138] The homology to members of the B7 family of ligands indicates that the polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis, detection and/or treatment of diseases and/or disorders involving immune system activation, stimulation and/or surveillance, particularly as relating to T cells and/or neutrophils. In particular, the translation product of the B7-H9 gene may be involved in the costimulation of T cells, binding to ICOS, and/or may play a role in modulation of the expression of particular cytokines, for example.

[139] Expression within small intestine and colon tissues suggests that polynucleotides, translation products and antibodies corresponding to this gene are useful for the diagnosis and/or treatment of disorders involving the small intestine. This may include diseases associated with digestion and food absorption, as well as hematopoietic disorders involving the Peyer's patches of the small intestine, or other hematopoietic cells and tissues within the body. Similarly, expression of this gene product in colon and colon cancer tissues suggests again involvement in digestion, processing, and elimination of food, as well as a potential role for this gene as a diagnostic marker or causative agent in the development of colon cancer, and cancer in general. Additionally, translation products corresponding to this gene, as well as antibodies directed against these translation products, may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 4

[140] For purposes of this application, this gene and its corresponding translation product are known as the B7-H11 gene and B7-H11 protein. This protein is believed to reside as a cell-surface molecule, and the transmembrane domain of this protein is believed to approximately embody the following preferred amino acid residues: TASPWMVSMTVILAVFIIFMAVSICC (SEQ ID NO: 38). Polynucleotides encoding these polypeptides are also encompassed by the invention, as are antibodies that bind one or more of these polypeptides. Moreover, fragments and variants of these polypeptides (e.g., fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or

the complement thereof) are encompassed by the invention. Antibodies that bind these fragments and variants of the invention are also encompassed by the invention. Polynucleotides encoding these fragments and variants are also encompassed by the invention. As one skilled in the art would understand, the transmembrane domain was predicted using computer analysis, and the transmembrane domain may vary by one, two, three, four, five, six, seven, eight, nine, and/or ten amino acids from the N and C-termini of the predicted transmembrane domain. The B7-H11 gene shares sequence homology with members of the B7 family of ligands (i.e., B7-H1 (See Genbank Accession AAF25807)). These proteins and their corresponding receptors play vital roles in the growth, differentiation, activation, proliferation and death of T cells. For example, some members of this family (i.e., B7-H1) are involved in costimulation of the T cell response, as well as inducing increased cytokine production, while other family members are involved in the negative regulation of the T cell response. Therefore, agonists and antagonists such as antibodies or small molecules directed against the B7-H11 gene are useful for treating T cell mediated immune system disorders, as well as disorders of other immune system cells, such as for example, neutrophils, macrophage, and leukocytes.

[141] Preferred polypeptides of the present invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, eight, nine, ten, eleven, or all eleven of the immunogenic epitopes of the B7-H11 protein shown in SEQ ID NO: 17 as residues: Ser-53 to Glu-59, Lys-78 to Gly-93, Ala-116 to Tyr-122, Gln-127 to Asp-133, Lys-153 to Ser-159, Lys-283 to Lys-289, Ser-292 to Glu-303, Glu-339 to Ser-362, Ala-373 to Asn-381, Glu-384 to Arg-392, and Asn-394 to His-419. Polynucleotides encoding these polypeptides are also encompassed by the invention, as are antibodies that bind one or more of these polypeptides. Moreover, fragments and variants of these polypeptides (e.g., fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof) are encompassed by the invention. Antibodies that bind these fragments and variants of the invention are also encompassed by the invention. Polynucleotides encoding these fragments and variants are also encompassed by the invention.

[142] In additional nonexclusive embodiments, polypeptides of the invention comprise, or alternatively consist of, an amino acid sequence selected from the group consisting of:

[143] The extracellular domain of the B7-H11 protein: MEPAAALHFSRPASLLLLLSLCALVSAQFTVVGPANPILAMVGENTTLRCHLSPEKNAEDMEVRWFRSQFSPAVFVYKGGRERTEEQMEEYRGRITFVSKDINRGSVALVIHNVTAQENGIYRCYFQEGRSYDEAILRLVVAGLGSKPLIEIKAQEDGSIWLECISGGWYPEPLTVWRDPYGEVVPALKEVSIADADGLFMVTTAVIIRDKYVRNVSCSVNNTLLGQEKETVIFIPESFMPSASPWMVALAVIL (SEQ ID NO: 39),

[144] The mature extracellular domain of the B7-H11 protein: QFTVVGPANPILAMVGENTTLRCHLSPEKNAEDMEVRWFRSQFSPAVFVYKGGRERTEEQMEEYRGRITFVSKDINRGSVALVIHNVTAQENGIYRCYFQEGRSYDEAILRLVVAGLGSKPLIEIKAQEDGSIWLECISGGWYPEPLTVWRDPYGEVVPALKEVSIADADGLFMVTTAVIIRDKYVRNVSCSVNNTLLGQEKETVIFIPESFMPSASPWMVALAVIL (SEQ ID NO: 40), and/or

[145] The leader sequence of the B7-H11 protein: MEPAAALHFSRPASLLLLLSLCALVSA (SEQ ID NO: 41). Polynucleotides encoding these polypeptides are also encompassed by the invention, as are antibodies that bind one or more of these polypeptides. Moreover, fragments and variants of these polypeptides (e.g., fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof) are encompassed by the invention. Antibodies that bind these fragments and variants of the invention are also encompassed by the invention. Polynucleotides encoding these fragments and variants are also encompassed by the invention.

[146] Also preferred are polypeptides comprising, or alternatively consisting of, fragments of the mature extracellular portion of the B7-H11 protein demonstrating functional activity (SEQ ID NO: 40). Polynucleotides encoding these polypeptides are also encompassed by the invention, as are antibodies that bind one or more of these polypeptides. Moreover, fragments and variants of these polypeptides (e.g., fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof) are encompassed by the invention. Antibodies that bind these fragments and variants

of the invention are also encompassed by the invention. Polynucleotides encoding these fragments and variants are also encompassed by the invention.

[147] By functional activity is meant, a polypeptide fragment capable of displaying one or more known functional activities associated with the full-length (complete) B7-H11 protein. Such functional activities include, but are not limited to, biological activity (e.g., T cell costimulatory activity, ability to bind ICOS, CD28 or CTLA4, and ability to induce or inhibit cytokine production), antigenicity [ability to bind (or compete with a B7-H11 polypeptide for binding) to an anti-B7-H11 antibody], immunogenicity (ability to generate antibody which binds to a B7-H11 polypeptide), ability to form multimers with B7-H11 polypeptides of the invention, and ability to bind to a receptor for a B7-H11 polypeptide.

[148] Figures 7A-D show the nucleotide (SEQ ID NO: 5) and deduced amino acid sequence (SEQ ID NO: 17) corresponding to this gene. Figure 8 shows an analysis of the amino acid sequence (SEQ ID NO: 17). Alpha, beta, turn and coil regions; hydrophilicity and hydrophobicity; amphipathic regions; flexible regions; antigenic index and surface probability are shown, and all were generated using the default settings of the recited computer algorithyms. In the "Antigenic Index or Jameson-Wolf" graph, the positive peaks indicate locations of the highly antigenic regions of the protein, i.e., regions from which epitope-bearing peptides of the invention can be obtained. Polypeptides comprising, or alternatively consisting of, domains defined by these graphs are contemplated by the present invention, as are polynucleotides encoding these polypeptides. The data presented in Figure 8 are also represented in tabular form in Table 6. The columns are labeled with the headings "Res", "Position", and Roman Numerals I-XIV. The column headings refer to the following features of the amino acid sequence presented in Figure 8, and Table 6: "Res": amino acid residue of SEQ ID NO: 17 and Figures 7A-C; "Position": position of the corresponding residue within SEQ ID NO: 17 and Figures 7A-C; I: Alpha, Regions - Garnier-Robson; II: Alpha, Regions - Chou-Fasman; III: Beta, Regions - Garnier-Robson; IV: Beta, Regions - Chou-Fasman; V: Turn, Regions - Garnier-Robson; VI: Turn, Regions - Chou-Fasman; VII: Coil, Regions - Garnier-Robson; VIII: Hydrophilicity Plot - Kyte-Doolittle; IX: Hydrophobicity Plot - Hopp-Woods; X: Alpha, Amphipathic Regions - Eisenberg; XI: Beta, Amphipathic Regions - Eisenberg; XII: Flexible Regions - Karplus-Schulz; XIII: Antigenic Index - Jameson-Wolf; and XIV: Surface Probability Plot - Emini. Preferred embodiments of the invention in this regard include fragments that comprise, or alternatively consisting of,

one or more of the following regions: alpha-helix and alpha-helix forming regions ("alpha-regions"), beta-sheet and beta-sheet forming regions ("beta-regions"), turn and turn-forming regions ("turn-regions"), coil and coil-forming regions ("coil-regions"), hydrophilic regions, hydrophobic regions, alpha amphipathic regions, beta amphipathic regions, flexible regions, surface-forming regions and high antigenic index regions. The data representing the structural or functional attributes of the protein set forth in Figure 8 and/or Table 6, as described above, was generated using the various modules and algorithms of the DNA*STAR set on default parameters. In a preferred embodiment, the data presented in columns VIII, IX, XIII, and XIV of Table 6 can be used to determine regions of the protein which exhibit a high degree of potential for antigenicity. Regions of high antigenicity are determined from the data presented in columns VIII, IX, XIII, and/or XIV by choosing values which represent regions of the polypeptide which are likely to be exposed on the surface of the polypeptide in an environment in which antigen recognition may occur in the process of initiation of an immune response. Certain preferred regions in these regards are set out in Figure 8, but may, as shown in Table 6, be represented or identified by using tabular representations of the data presented in Figure 8. The DNA*STAR computer algorithm used to generate Figure 8 (set on the original default parameters) was used to present the data in Figure 8 in a tabular format (See Table 6). The tabular format of the data in Figure 8 (See Table 6) is used to easily determine specific boundaries of a preferred region.

[149] The present invention is further directed to fragments of the polynucleotide sequences described herein. By a fragment of, for example, the polynucleotide sequence of a deposited cDNA or the nucleotide sequence shown in SEQ ID NO: 5, is intended polynucleotide fragments at least about 15nt, and more preferably at least about 20 nt, at least about 25nt, still more preferably at least about 30 nt, at least about 35nt, and even more preferably, at least about 40 nt in length, at least about 45nt in length, at least about 50nt in length, at least about 60nt in length, at least about 70nt in length, at least about 80nt in length, at least about 90nt in length, at least about 100nt in length, at least about 125nt in length, at least about 150nt in length, at least about 175nt in length, which are useful as diagnostic probes and primers as discussed herein. Of course, larger fragments 200-1500 nt in length are also useful according to the present invention, as are fragments corresponding to most, if not all, of the nucleotide sequence of a deposited cDNA or as shown in SEQ ID NO: 5. By a fragment at least 20 nt in length, for example, is intended fragments which include 20 or

more contiguous bases from the nucleotide sequence of a deposited cDNA or the nucleotide sequence as shown in SEQ ID NO: 5. In this context "about" includes the particularly recited size, an sizes larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Representative examples of polynucleotide fragments of the invention include, for example, fragments that comprise, or alternatively, consist of, a sequence from about nucleotide 1 to about 50, from about 51 to about 100, from about 101 to about 150, from about 151 to about 200, from about 201 to about 250, from about 251 to about 300, from about 301 to about 350, from about 351 to about 400, from about 401 to about 450, from about 451 to about 500, and from about 501 to about 550, and from about 551 to about 600, from about 601 to about 650, from about 651 to about 700, from about 701 to about 750, from about 751 to about 800, and from about 801 to about 860, of SEQ ID NO: 5, or the complementary strand thereto, or the cDNA contained in a deposited clone. In this context "about" includes the particularly recited ranges, and ranges larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. In additional embodiments, the polynucleotides of the invention encode functional attributes of the corresponding protein.

[150] Preferred polypeptide fragments of the invention comprise, or alternatively consist of, the secreted protein having a continuous series of deleted residues from the amino or the carboxy terminus, or both. Particularly, N-terminal deletions of the polypeptide can be described by the general formula m-454 where m is an integer from 2 to 449, where m corresponds to the position of the amino acid residue identified in SEQ ID NO: 17. More in particular, the invention provides polynucleotides encoding polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group: E-2 to L-454; P-3 to L-454; A-4 to L-454; A-5 to L-454; A-6 to L-454; L-7 to L-454; H-8 to L-454; F-9 to L-454; S-10 to L-454; R-11 to L-454; P-12 to L-454; A-13 to L-454; S-14 to L-454; L-15 to L-454; L-16 to L-454; L-17 to L-454; L-18 to L-454; L-19 to L-454; S-20 to L-454; L-21 to L-454; C-22 to L-454; A-23 to L-454; L-24 to L-454; V-25 to L-454; S-26 to L-454; A-27 to L-454; Q-28 to L-454; F-29 to L-454; T-30 to L-454; V-31 to L-454; V-32 to L-454; G-33 to L-454; P-34 to L-454; A-35 to L-454; N-36 to L-454; P-37 to L-454; I-38 to L-454; L-39 to L-454; A-40 to L-454; M-41 to L-454; V-42 to L-454; G-43 to L-454; E-44 to L-454; N-45 to L-454; T-46 to L-454; T-47 to L-454; L-48 to L-454; R-49 to L-454; C-50 to L-454; H-51 to L-454; L-52 to L-454; S-53 to L-454; P-54 to L-454; E-55 to L-454; K-56 to L-454; N-57 to L-454; A-58 to L-454; E-59 to L-454; D-60 to L-454; M-61 to L-454; E-62 to L-454; V-63 to

L-454; R-64 to L-454; W-65 to L-454; F-66 to L-454; R-67 to L-454; S-68 to L-454; Q-69 to L-454; F-70 to L-454; S-71 to L-454; P-72 to L-454; A-73 to L-454; V-74 to L-454; F-75 to L-454; V-76 to L-454; Y-77 to L-454; K-78 to L-454; G-79 to L-454; G-80 to L-454; R-81 to L-454; E-82 to L-454; R-83 to L-454; T-84 to L-454; E-85 to L-454; E-86 to L-454; Q-87 to L-454; M-88 to L-454; E-89 to L-454; E-90 to L-454; Y-91 to L-454; R-92 to L-454; G-93 to L-454; R-94 to L-454; I-95 to L-454; T-96 to L-454; F-97 to L-454; V-98 to L-454; S-99 to L-454; K-100 to L-454; D-101 to L-454; I-102 to L-454; N-103 to L-454; R-104 to L-454; G-105 to L-454; S-106 to L-454; V-107 to L-454; A-108 to L-454; L-109 to L-454; V-110 to L-454; I-111 to L-454; H-112 to L-454; N-113 to L-454; V-114 to L-454; T-115 to L-454; A-116 to L-454; Q-117 to L-454; E-118 to L-454; N-119 to L-454; G-120 to L-454; I-121 to L-454; Y-122 to L-454; R-123 to L-454; C-124 to L-454; Y-125 to L-454; F-126 to L-454; Q-127 to L-454; E-128 to L-454; G-129 to L-454; R-130 to L-454; S-131 to L-454; Y-132 to L-454; D-133 to L-454; E-134 to L-454; A-135 to L-454; I-136 to L-454; L-137 to L-454; R-138 to L-454; L-139 to L-454; V-140 to L-454; V-141 to L-454; A-142 to L-454; G-143 to L-454; L-144 to L-454; G-145 to L-454; S-146 to L-454; K-147 to L-454; P-148 to L-454; L-149 to L-454; I-150 to L-454; E-151 to L-454; I-152 to L-454; K-153 to L-454; A-154 to L-454; Q-155 to L-454; E-156 to L-454; D-157 to L-454; G-158 to L-454; S-159 to L-454; I-160 to L-454; W-161 to L-454; L-162 to L-454; E-163 to L-454; C-164 to L-454; I-165 to L-454; S-166 to L-454; G-167 to L-454; G-168 to L-454; W-169 to L-454; Y-170 to L-454; P-171 to L-454; E-172 to L-454; P-173 to L-454; L-174 to L-454; T-175 to L-454; V-176 to L-454; W-177 to L-454; R-178 to L-454; D-179 to L-454; P-180 to L-454; Y-181 to L-454; G-182 to L-454; E-183 to L-454; V-184 to L-454; V-185 to L-454; P-186 to L-454; A-187 to L-454; L-188 to L-454; K-189 to L-454; E-190 to L-454; V-191 to L-454; S-192 to L-454; I-193 to L-454; A-194 to L-454; D-195 to L-454; A-196 to L-454; D-197 to L-454; G-198 to L-454; L-199 to L-454; F-200 to L-454; M-201 to L-454; V-202 to L-454; T-203 to L-454; T-204 to L-454; A-205 to L-454; V-206 to L-454; I-207 to L-454; I-208 to L-454; R-209 to L-454; D-210 to L-454; K-211 to L-454; Y-212 to L-454; V-213 to L-454; R-214 to L-454; N-215 to L-454; V-216 to L-454; S-217 to L-454; C-218 to L-454; S-219 to L-454; V-220 to L-454; N-221 to L-454; N-222 to L-454; T-223 to L-454; L-224 to L-454; L-225 to L-454; G-226 to L-454; Q-227 to L-454; E-228 to L-454; K-229 to L-454; E-230 to L-454; T-231 to L-454; V-232 to L-454; I-233 to L-454; F-234 to L-454; I-235 to L-454; P-236 to L-454; E-237 to L-454; S-238 to L-454; F-239 to L-454; M-240 to L-454; P-241 to L-454; S-242 to L-

454; A-243 to L-454; S-244 to L-454; P-245 to L-454; W-246 to L-454; M-247 to L-454; V-248 to L-454; A-249 to L-454; L-250 to L-454; A-251 to L-454; V-252 to L-454; I-253 to L-454; L-254 to L-454; T-255 to L-454; A-256 to L-454; S-257 to L-454; P-258 to L-454; W-259 to L-454; M-260 to L-454; V-261 to L-454; S-262 to L-454; M-263 to L-454; T-264 to L-454; V-265 to L-454; I-266 to L-454; L-267 to L-454; A-268 to L-454; V-269 to L-454; F-270 to L-454; I-271 to L-454; I-272 to L-454; F-273 to L-454; M-274 to L-454; A-275 to L-454; V-276 to L-454; S-277 to L-454; I-278 to L-454; C-279 to L-454; C-280 to L-454; I-281 to L-454; K-282 to L-454; K-283 to L-454; L-284 to L-454; Q-285 to L-454; R-286 to L-454; E-287 to L-454; K-288 to L-454; K-289 to L-454; I-290 to L-454; L-291 to L-454; S-292 to L-454; G-293 to L-454; E-294 to L-454; K-295 to L-454; K-296 to L-454; V-297 to L-454; E-298 to L-454; Q-299 to L-454; E-300 to L-454; E-301 to L-454; K-302 to L-454; E-303 to L-454; I-304 to L-454; A-305 to L-454; Q-306 to L-454; Q-307 to L-454; L-308 to L-454; Q-309 to L-454; E-310 to L-454; E-311 to L-454; L-312 to L-454; R-313 to L-454; W-314 to L-454; R-315 to L-454; R-316 to L-454; T-317 to L-454; F-318 to L-454; L-319 to L-454; H-320 to L-454; A-321 to L-454; A-322 to L-454; D-323 to L-454; V-324 to L-454; V-325 to L-454; L-326 to L-454; D-327 to L-454; P-328 to L-454; D-329 to L-454; T-330 to L-454; A-331 to L-454; H-332 to L-454; P-333 to L-454; E-334 to L-454; L-335 to L-454; F-336 to L-454; L-337 to L-454; S-338 to L-454; E-339 to L-454; D-340 to L-454; R-341 to L-454; R-342 to L-454; S-343 to L-454; V-344 to L-454; R-345 to L-454; R-346 to L-454; G-347 to L-454; P-348 to L-454; Y-349 to L-454; R-350 to L-454; Q-351 to L-454; R-352 to L-454; V-353 to L-454; P-354 to L-454; D-355 to L-454; N-356 to L-454; P-357 to L-454; E-358 to L-454; R-359 to L-454; F-360 to L-454; D-361 to L-454; S-362 to L-454; Q-363 to L-454; P-364 to L-454; C-365 to L-454; V-366 to L-454; L-367 to L-454; G-368 to L-454; W-369 to L-454; E-370 to L-454; S-371 to L-454; F-372 to L-454; A-373 to L-454; S-374 to L-454; G-375 to L-454; K-376 to L-454; H-377 to L-454; Y-378 to L-454; R-379 to L-454; G-380 to L-454; N-381 to L-454; F-382 to L-454; T-383 to L-454; E-384 to L-454; W-385 to L-454; G-386 to L-454; P-387 to L-454; T-388 to L-454; R-389 to L-454; A-390 to L-454; Y-391 to L-454; R-392 to L-454; I-393 to L-454; N-394 to L-454; S-395 to L-454; L-396 to L-454; D-397 to L-454; S-398 to L-454; Q-399 to L-454; P-400 to L-454; C-401 to L-454; R-402 to L-454; K-403 to L-454; P-404 to L-454; W-405 to L-454; P-406 to L-454; S-407 to L-454; Q-408 to L-454; Q-409 to L-454; P-410 to L-454; P-411 to L-454; H-412 to L-454; N-413 to L-454; P-414 to L-454; P-415 to L-454; N-416 to L-454; E-417 to L-454; R-418 to L-454; H-

419 to L-454; A-420 to L-454; L-421 to L-454; L-422 to L-454; P-423 to L-454; S-424 to L-454; G-425 to L-454; H-426 to L-454; V-427 to L-454; R-428 to L-454; E-429 to L-454; H-430 to L-454; L-431 to L-454; P-432 to L-454; A-433 to L-454; A-434 to L-454; F-435 to L-454; F-436 to L-454; T-437 to L-454; P-438 to L-454; T-439 to L-454; P-440 to L-454; A-441 to L-454; L-442 to L-454; C-443 to L-454; P-444 to L-454; S-445 to L-454; F-446 to L-454; L-447 to L-454; L-448 to L-454; and/or L-449 to L-454 of SEQ ID NO: 17. Polynucleotides encoding these polypeptides are also encompassed by the invention, as are antibodies that bind one or more of these polypeptides. Moreover, fragments and variants of these polypeptides (e.g., fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof) are encompassed by the invention. Antibodies that bind these fragments and variants of the invention are also encompassed by the invention. Polynucleotides encoding these fragments and variants are also encompassed by the invention.

[151] Accordingly, the present invention further provides polypeptides having one or more residues deleted from the carboxy terminus of the amino acid sequence of the polypeptide shown in Figures 7A-C (SEQ ID NO: 17), as described by the general formula 1-n, where n is an integer from 7 to 453, where n corresponds to the position of the amino acid residue identified in SEQ ID NO: 17. Additionally, the invention provides polynucleotides encoding polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the following group of C-terminal deletions: M-1 to W-453; M-1 to L-452; M-1 to S-451; M-1 to T-450; M-1 to L-449; M-1 to L-448; M-1 to L-447; M-1 to F-446; M-1 to S-445; M-1 to P-444; M-1 to C-443; M-1 to L-442; M-1 to A-441; M-1 to P-440; M-1 to T-439; M-1 to P-438; M-1 to T-437; M-1 to F-436; M-1 to F-435; M-1 to A-434; M-1 to A-433; M-1 to P-432; M-1 to L-431; M-1 to H-430; M-1 to E-429; M-1 to R-428; M-1 to V-427; M-1 to H-426; M-1 to G-425; M-1 to S-424; M-1 to P-423; M-1 to L-422; M-1 to L-421; M-1 to A-420; M-1 to H-419; M-1 to R-418; M-1 to E-417; M-1 to N-416; M-1 to P-415; M-1 to P-414; M-1 to N-413; M-1 to H-412; M-1 to P-411; M-1 to P-410; M-1 to Q-409; M-1 to Q-408; M-1 to S-407; M-1 to P-406; M-1 to W-405; M-1 to P-404; M-1 to K-403; M-1 to R-402; M-1 to C-401; M-1 to P-400; M-1 to Q-399; M-1 to S-398; M-1 to D-397; M-1 to L-396; M-1 to S-395; M-1 to N-394; M-1 to I-393; M-1 to R-392; M-1 to Y-391;

M-1 to A-390; M-1 to R-389; M-1 to T-388; M-1 to P-387; M-1 to G-386; M-1 to W-385; M-1 to E-384; M-1 to T-383; M-1 to F-382; M-1 to N-381; M-1 to G-380; M-1 to R-379; M-1 to Y-378; M-1 to H-377; M-1 to K-376; M-1 to G-375; M-1 to S-374; M-1 to A-373; M-1 to F-372; M-1 to S-371; M-1 to E-370; M-1 to W-369; M-1 to G-368; M-1 to L-367; M-1 to V-366; M-1 to C-365; M-1 to P-364; M-1 to Q-363; M-1 to S-362; M-1 to D-361; M-1 to F-360; M-1 to R-359; M-1 to E-358; M-1 to P-357; M-1 to N-356; M-1 to D-355; M-1 to P-354; M-1 to V-353; M-1 to R-352; M-1 to Q-351; M-1 to R-350; M-1 to Y-349; M-1 to P-348; M-1 to G-347; M-1 to R-346; M-1 to R-345; M-1 to V-344; M-1 to S-343; M-1 to R-342; M-1 to R-341; M-1 to D-340; M-1 to E-339; M-1 to S-338; M-1 to L-337; M-1 to F-336; M-1 to L-335; M-1 to E-334; M-1 to P-333; M-1 to H-332; M-1 to A-331; M-1 to T-330; M-1 to D-329; M-1 to P-328; M-1 to D-327; M-1 to L-326; M-1 to V-325; M-1 to V-324; M-1 to D-323; M-1 to A-322; M-1 to A-321; M-1 to H-320; M-1 to L-319; M-1 to F-318; M-1 to T-317; M-1 to R-316; M-1 to R-315; M-1 to W-314; M-1 to R-313; M-1 to L-312; M-1 to E-311; M-1 to E-310; M-1 to Q-309; M-1 to L-308; M-1 to Q-307; M-1 to Q-306; M-1 to A-305; M-1 to I-304; M-1 to E-303; M-1 to K-302; M-1 to E-301; M-1 to E-300; M-1 to Q-299; M-1 to E-298; M-1 to V-297; M-1 to K-296; M-1 to K-295; M-1 to E-294; M-1 to G-293; M-1 to S-292; M-1 to L-291; M-1 to I-290; M-1 to K-289; M-1 to K-288; M-1 to E-287; M-1 to R-286; M-1 to Q-285; M-1 to L-284; M-1 to K-283; M-1 to K-282; M-1 to I-281; M-1 to C-280; M-1 to C-279; M-1 to I-278; M-1 to S-277; M-1 to V-276; M-1 to A-275; M-1 to M-274; M-1 to F-273; M-1 to I-272; M-1 to I-271; M-1 to F-270; M-1 to V-269; M-1 to A-268; M-1 to L-267; M-1 to I-266; M-1 to V-265; M-1 to T-264; M-1 to M-263; M-1 to S-262; M-1 to V-261; M-1 to M-260; M-1 to W-259; M-1 to P-258; M-1 to S-257; M-1 to A-256; M-1 to T-255; M-1 to L-254; M-1 to I-253; M-1 to V-252; M-1 to A-251; M-1 to L-250; M-1 to A-249; M-1 to V-248; M-1 to M-247; M-1 to W-246; M-1 to P-245; M-1 to S-244; M-1 to A-243; M-1 to S-242; M-1 to P-241; M-1 to M-240; M-1 to F-239; M-1 to S-238; M-1 to E-237; M-1 to P-236; M-1 to I-235; M-1 to F-234; M-1 to I-233; M-1 to V-232; M-1 to T-231; M-1 to E-230; M-1 to K-229; M-1 to E-228; M-1 to Q-227; M-1 to G-226; M-1 to L-225; M-1 to L-224; M-1 to T-223; M-1 to N-222; M-1 to N-221; M-1 to V-220; M-1 to S-219; M-1 to C-218; M-1 to S-217; M-1 to V-216; M-1 to N-215; M-1 to R-214; M-1 to V-213; M-1 to Y-212; M-1 to K-211; M-1 to D-210; M-1 to R-209; M-1 to I-208; M-1 to I-207; M-1 to V-206; M-1 to A-205; M-1 to T-204; M-1 to T-203; M-1 to V-202; M-1 to M-201; M-1 to F-200; M-1 to L-199; M-1 to G-198; M-1 to D-197; M-1 to A-196; M-1 to D-195; M-

1 to A-194; M-1 to I-193; M-1 to S-192; M-1 to V-191; M-1 to E-190; M-1 to K-189; M-1 to L-188; M-1 to A-187; M-1 to P-186; M-1 to V-185; M-1 to V-184; M-1 to E-183; M-1 to G-182; M-1 to Y-181; M-1 to P-180; M-1 to D-179; M-1 to R-178; M-1 to W-177; M-1 to V-176; M-1 to T-175; M-1 to L-174; M-1 to P-173; M-1 to E-172; M-1 to P-171; M-1 to Y-170; M-1 to W-169; M-1 to G-168; M-1 to G-167; M-1 to S-166; M-1 to I-165; M-1 to C-164; M-1 to E-163; M-1 to L-162; M-1 to W-161; M-1 to I-160; M-1 to S-159; M-1 to G-158; M-1 to D-157; M-1 to E-156; M-1 to Q-155; M-1 to A-154; M-1 to K-153; M-1 to I-152; M-1 to E-151; M-1 to I-150; M-1 to L-149; M-1 to P-148; M-1 to K-147; M-1 to S-146; M-1 to G-145; M-1 to L-144; M-1 to G-143; M-1 to A-142; M-1 to V-141; M-1 to V-140; M-1 to L-139; M-1 to R-138; M-1 to L-137; M-1 to I-136; M-1 to A-135; M-1 to E-134; M-1 to D-133; M-1 to Y-132; M-1 to S-131; M-1 to R-130; M-1 to G-129; M-1 to E-128; M-1 to Q-127; M-1 to F-126; M-1 to Y-125; M-1 to C-124; M-1 to R-123; M-1 to Y-122; M-1 to I-121; M-1 to G-120; M-1 to N-119; M-1 to E-118; M-1 to Q-117; M-1 to A-116; M-1 to T-115; M-1 to V-114; M-1 to N-113; M-1 to H-112; M-1 to I-111; M-1 to V-110; M-1 to L-109; M-1 to A-108; M-1 to V-107; M-1 to S-106; M-1 to G-105; M-1 to R-104; M-1 to N-103; M-1 to I-102; M-1 to D-101; M-1 to K-100; M-1 to S-99; M-1 to V-98; M-1 to F-97; M-1 to T-96; M-1 to I-95; M-1 to R-94; M-1 to G-93; M-1 to R-92; M-1 to Y-91; M-1 to E-90; M-1 to E-89; M-1 to M-88; M-1 to Q-87; M-1 to E-86; M-1 to E-85; M-1 to T-84; M-1 to R-83; M-1 to E-82; M-1 to R-81; M-1 to G-80; M-1 to G-79; M-1 to K-78; M-1 to Y-77; M-1 to V-76; M-1 to F-75; M-1 to V-74; M-1 to A-73; M-1 to P-72; M-1 to S-71; M-1 to F-70; M-1 to Q-69; M-1 to S-68; M-1 to R-67; M-1 to F-66; M-1 to W-65; M-1 to R-64; M-1 to V-63; M-1 to E-62; M-1 to M-61; M-1 to D-60; M-1 to E-59; M-1 to A-58; M-1 to N-57; M-1 to K-56; M-1 to E-55; M-1 to P-54; M-1 to S-53; M-1 to L-52; M-1 to H-51; M-1 to C-50; M-1 to R-49; M-1 to L-48; M-1 to T-47; M-1 to T-46; M-1 to N-45; M-1 to E-44; M-1 to G-43; M-1 to V-42; M-1 to M-41; M-1 to A-40; M-1 to L-39; M-1 to I-38; M-1 to P-37; M-1 to N-36; M-1 to A-35; M-1 to P-34; M-1 to G-33; M-1 to V-32; M-1 to V-31; M-1 to T-30; M-1 to F-29; M-1 to Q-28; M-1 to A-27; M-1 to S-26; M-1 to V-25; M-1 to L-24; M-1 to A-23; M-1 to C-22; M-1 to L-21; M-1 to S-20; M-1 to L-19; M-1 to L-18; M-1 to L-17; M-1 to L-16; M-1 to L-15; M-1 to S-14; M-1 to A-13; M-1 to P-12; M-1 to R-11; M-1 to S-10; M-1 to F-9; M-1 to H-8; and/or M-1 to L-7 of SEQ ID NO: 17. Polynucleotides encoding these polypeptides are also encompassed by the invention, as are antibodies that bind one or more of these polypeptides. Moreover, fragments and variants of these polypeptides (e.g., fragments as

described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof) are encompassed by the invention. Antibodies that bind these fragments and variants of the invention are also encompassed by the invention. Polynucleotides encoding these fragments and variants are also encompassed by the invention.

[152] Also as mentioned above, even if deletion of one or more amino acids from the C-terminus of a protein results in modification of loss of one or more biological functions of the protein (e.g., ability to inhibit the Mixed Lymphocyte Reaction), other functional activities (e.g., biological activities, ability to multimerize, ability to bind receptor, ability to generate antibodies, ability to bind antibodies) may still be retained. For example, the ability of the shortened polypeptide to induce and/or bind to antibodies which recognize the complete or mature forms of the polypeptide generally will be retained when less than the majority of the residues of the complete or mature polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a polypeptide with a large number of deleted C-terminal amino acid residues may retain some biological or immunogenic activities. In fact, peptides composed of as few as six amino acid residues may often evoke an immune response.

[153] More in particular, the invention provides polynucleotides encoding polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group of N-terminal deletions of the mature extracellular portion of the B7-H11 protein (SEQ ID NO: 40): F-29 to L-254; T-30 to L-254; V-31 to L-254; V-32 to L-254; G-33 to L-254; P-34 to L-254; A-35 to L-254; N-36 to L-254; P-37 to L-254; I-38 to L-254; L-39 to L-254; A-40 to L-254; M-41 to L-254; V-42 to L-254; G-43 to L-254; E-44 to L-254; N-45 to L-254; T-46 to L-254; T-47 to L-254; L-48 to L-254; R-49 to L-254; C-50 to L-254; H-51 to L-254; L-52 to L-254; S-53 to L-254; P-54 to L-254; E-55 to L-254; K-56 to L-254; N-57 to L-254; A-58 to L-254; E-59 to L-254; D-60 to L-254; M-61 to L-254; E-62 to L-254; V-63 to L-254; R-64 to L-254; W-65 to L-254; F-66 to L-254; R-67 to L-254; S-68 to L-254; Q-69 to L-254; F-70 to L-254; S-71 to L-254; P-72 to L-254; A-73 to L-254; V-74 to L-254; F-75 to L-254; V-76 to

L-254; Y-77 to L-254; K-78 to L-254; G-79 to L-254; G-80 to L-254; R-81 to L-254; E-82 to L-254; R-83 to L-254; T-84 to L-254; E-85 to L-254; E-86 to L-254; Q-87 to L-254; M-88 to L-254; E-89 to L-254; E-90 to L-254; Y-91 to L-254; R-92 to L-254; G-93 to L-254; R-94 to L-254; I-95 to L-254; T-96 to L-254; F-97 to L-254; V-98 to L-254; S-99 to L-254; K-100 to L-254; D-101 to L-254; I-102 to L-254; N-103 to L-254; R-104 to L-254; G-105 to L-254; S-106 to L-254; V-107 to L-254; A-108 to L-254; L-109 to L-254; V-110 to L-254; I-111 to L-254; H-112 to L-254; N-113 to L-254; V-114 to L-254; T-115 to L-254; A-116 to L-254; Q-117 to L-254; E-118 to L-254; N-119 to L-254; G-120 to L-254; I-121 to L-254; Y-122 to L-254; R-123 to L-254; C-124 to L-254; Y-125 to L-254; F-126 to L-254; Q-127 to L-254; E-128 to L-254; G-129 to L-254; R-130 to L-254; S-131 to L-254; Y-132 to L-254; D-133 to L-254; E-134 to L-254; A-135 to L-254; I-136 to L-254; L-137 to L-254; R-138 to L-254; L-139 to L-254; V-140 to L-254; V-141 to L-254; A-142 to L-254; G-143 to L-254; L-144 to L-254; G-145 to L-254; S-146 to L-254; K-147 to L-254; P-148 to L-254; L-149 to L-254; I-150 to L-254; E-151 to L-254; I-152 to L-254; K-153 to L-254; A-154 to L-254; Q-155 to L-254; E-156 to L-254; D-157 to L-254; G-158 to L-254; S-159 to L-254; I-160 to L-254; W-161 to L-254; L-162 to L-254; E-163 to L-254; C-164 to L-254; I-165 to L-254; S-166 to L-254; G-167 to L-254; G-168 to L-254; W-169 to L-254; Y-170 to L-254; P-171 to L-254; E-172 to L-254; P-173 to L-254; L-174 to L-254; T-175 to L-254; V-176 to L-254; W-177 to L-254; R-178 to L-254; D-179 to L-254; P-180 to L-254; Y-181 to L-254; G-182 to L-254; E-183 to L-254; V-184 to L-254; V-185 to L-254; P-186 to L-254; A-187 to L-254; L-188 to L-254; K-189 to L-254; E-190 to L-254; V-191 to L-254; S-192 to L-254; I-193 to L-254; A-194 to L-254; D-195 to L-254; A-196 to L-254; D-197 to L-254; G-198 to L-254; L-199 to L-254; F-200 to L-254; M-201 to L-254; V-202 to L-254; T-203 to L-254; T-204 to L-254; A-205 to L-254; V-206 to L-254; I-207 to L-254; I-208 to L-254; R-209 to L-254; D-210 to L-254; K-211 to L-254; Y-212 to L-254; V-213 to L-254; R-214 to L-254; N-215 to L-254; V-216 to L-254; S-217 to L-254; C-218 to L-254; S-219 to L-254; V-220 to L-254; N-221 to L-254; N-222 to L-254; T-223 to L-254; L-224 to L-254; L-225 to L-254; G-226 to L-254; Q-227 to L-254; E-228 to L-254; K-229 to L-254; E-230 to L-254; T-231 to L-254; V-232 to L-254; I-233 to L-254; F-234 to L-254; I-235 to L-254; P-236 to L-254; E-237 to L-254; S-238 to L-254; F-239 to L-254; M-240 to L-254; P-241 to L-254; S-242 to L-254; A-243 to L-254; S-244 to L-254; P-245 to L-254; W-246 to L-254; M-247 to L-254; V-248 to L-254; and/or A-249 to L-254 of SEQ ID NO: 17. Polynucleotides encoding these polypeptides are

also encompassed by the invention, as are antibodies that bind one or more of these polypeptides. Moreover, fragments and variants of these polypeptides (e.g., fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof) are encompassed by the invention. Antibodies that bind these fragments and variants of the invention are also encompassed by the invention. Polynucleotides encoding these fragments and variants are also encompassed by the invention.

[154] Additionally, the invention provides polynucleotides encoding polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group of C-terminal deletions of the mature extracellular portion of the B7-H11 protein (SEQ ID NO: 40): Q-28 to I-253; Q-28 to V-252; Q-28 to A-251; Q-28 to L-250; Q-28 to A-249; Q-28 to V-248; Q-28 to M-247; Q-28 to W-246; Q-28 to P-245; Q-28 to S-244; Q-28 to A-243; Q-28 to S-242; Q-28 to P-241; Q-28 to M-240; Q-28 to F-239; Q-28 to S-238; Q-28 to E-237; Q-28 to P-236; Q-28 to I-235; Q-28 to F-234; Q-28 to I-233; Q-28 to V-232; Q-28 to T-231; Q-28 to E-230; Q-28 to K-229; Q-28 to E-228; Q-28 to Q-227; Q-28 to G-226; Q-28 to L-225; Q-28 to L-224; Q-28 to T-223; Q-28 to N-222; Q-28 to N-221; Q-28 to V-220; Q-28 to S-219; Q-28 to C-218; Q-28 to S-217; Q-28 to V-216; Q-28 to N-215; Q-28 to R-214; Q-28 to V-213; Q-28 to Y-212; Q-28 to K-211; Q-28 to D-210; Q-28 to R-209; Q-28 to I-208; Q-28 to I-207; Q-28 to V-206; Q-28 to A-205; Q-28 to T-204; Q-28 to T-203; Q-28 to V-202; Q-28 to M-201; Q-28 to F-200; Q-28 to L-199; Q-28 to G-198; Q-28 to D-197; Q-28 to A-196; Q-28 to D-195; Q-28 to A-194; Q-28 to I-193; Q-28 to S-192; Q-28 to V-191; Q-28 to E-190; Q-28 to K-189; Q-28 to L-188; Q-28 to A-187; Q-28 to P-186; Q-28 to V-185; Q-28 to V-184; Q-28 to E-183; Q-28 to G-182; Q-28 to Y-181; Q-28 to P-180; Q-28 to D-179; Q-28 to R-178; Q-28 to W-177; Q-28 to V-176; Q-28 to T-175; Q-28 to L-174; Q-28 to P-173; Q-28 to E-172; Q-28 to P-171; Q-28 to Y-170; Q-28 to W-169; Q-28 to G-168; Q-28 to G-167; Q-28 to S-166; Q-28 to I-165; Q-28 to C-164; Q-28 to E-163; Q-28 to L-162; Q-28 to W-161; Q-28 to I-160; Q-28 to S-159; Q-28 to G-158; Q-28 to D-157; Q-28 to E-156; Q-28 to Q-155; Q-28 to A-154; Q-28 to K-153; Q-28 to I-152; Q-28 to E-151; Q-28 to I-150; Q-28 to L-149; Q-28 to P-148; Q-28 to K-147; Q-28 to S-146; Q-28 to G-145; Q-28 to L-144; Q-28 to G-143; Q-28 to A-142; Q-28 to V-141; Q-28 to V-140; Q-28 to L-139; Q-28 to R-138; Q-28 to

L-137; Q-28 to I-136; Q-28 to A-135; Q-28 to E-134; Q-28 to D-133; Q-28 to Y-132; Q-28 to S-131; Q-28 to R-130; Q-28 to G-129; Q-28 to E-128; Q-28 to Q-127; Q-28 to F-126; Q-28 to Y-125; Q-28 to C-124; Q-28 to R-123; Q-28 to Y-122; Q-28 to I-121; Q-28 to G-120; Q-28 to N-119; Q-28 to E-118; Q-28 to Q-117; Q-28 to A-116; Q-28 to T-115; Q-28 to V-114; Q-28 to N-113; Q-28 to H-112; Q-28 to I-111; Q-28 to V-110; Q-28 to L-109; Q-28 to A-108; Q-28 to V-107; Q-28 to S-106; Q-28 to G-105; Q-28 to R-104; Q-28 to N-103; Q-28 to I-102; Q-28 to D-101; Q-28 to K-100; Q-28 to S-99; Q-28 to V-98; Q-28 to F-97; Q-28 to T-96; Q-28 to I-95; Q-28 to R-94; Q-28 to G-93; Q-28 to R-92; Q-28 to Y-91; Q-28 to E-90; Q-28 to E-89; Q-28 to M-88; Q-28 to Q-87; Q-28 to E-86; Q-28 to E-85; Q-28 to T-84; Q-28 to R-83; Q-28 to E-82; Q-28 to R-81; Q-28 to G-80; Q-28 to G-79; Q-28 to K-78; Q-28 to Y-77; Q-28 to V-76; Q-28 to F-75; Q-28 to V-74; Q-28 to A-73; Q-28 to P-72; Q-28 to S-71; Q-28 to F-70; Q-28 to Q-69; Q-28 to S-68; Q-28 to R-67; Q-28 to F-66; Q-28 to W-65; Q-28 to R-64; Q-28 to V-63; Q-28 to E-62; Q-28 to M-61; Q-28 to D-60; Q-28 to E-59; Q-28 to A-58; Q-28 to N-57; Q-28 to K-56; Q-28 to E-55; Q-28 to P-54; Q-28 to S-53; Q-28 to L-52; Q-28 to H-51; Q-28 to C-50; Q-28 to R-49; Q-28 to L-48; Q-28 to T-47; Q-28 to T-46; Q-28 to N-45; Q-28 to E-44; Q-28 to G-43; Q-28 to V-42; Q-28 to M-41; Q-28 to A-40; Q-28 to L-39; Q-28 to I-38; Q-28 to P-37; Q-28 to N-36; Q-28 to A-35; and/or Q-28 to P-34 of SEQ ID NO: 17. Polynucleotides encoding these polypeptides are also encompassed by the invention, as are antibodies that bind one or more of these polypeptides. Moreover, fragments and variants of these polypeptides (e.g., fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof) are encompassed by the invention. Antibodies that bind these fragments and variants of the invention are also encompassed by the invention. Polynucleotides encoding these fragments and variants are also encompassed by the invention.

[155] In addition, any of the above listed N- or C-terminal deletions can be combined to produce a N- and C-terminal deleted polypeptide. The invention also provides polypeptides comprising, or alternatively consisting of, one or more amino acids deleted from both the amino and the carboxyl termini, which may be described generally as having residues m-n of SEQ ID NO: 17, where n and m are integers as described above. Fragments and/or variants of these polypeptides, such as, for example, fragments and/or variants as described herein, are

encompassed by the invention. Polynucleotides encoding these polypeptides (including fragments and/or variants) are also encompassed by the invention, as are antibodies that bind these polypeptides.

[156] The present invention is also directed to proteins containing polypeptides at least 80%, 85%, 90%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to a polypeptide sequence set forth herein as m-n. In preferred embodiments, the application is directed to proteins containing polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to polypeptides having the amino acid sequence of the specific N- and C-terminal deletions recited herein. Fragments and/or variants of these polypeptides, such as, for example, fragments and/or variants as described herein, are encompassed by the invention. Polynucleotides encoding these polypeptides (including fragments and/or variants) are also encompassed by the invention, as are antibodies that bind these polypeptides.

[157] Also included are polynucleotide sequences encoding a polypeptide consisting of a portion of the complete amino acid sequence encoded by a cDNA clone contained in ATCC Deposit No. PTA-2332, where this portion excludes any integer of amino acid residues from 1 to about 448 amino acids from the amino terminus of the complete amino acid sequence encoded by a cDNA clone contained in ATCC Deposit No. PTA-2332, or any integer of amino acid residues from 1 to about 448 amino acids from the carboxy terminus, or any combination of the above amino terminal and carboxy terminal deletions, of the complete amino acid sequence encoded by the cDNA clone contained in ATCC Deposit No. PTA-2332. Polypeptides encoded by these polynucleotides also are encompassed by the invention.

[158] As described herein or otherwise known in the art, the polynucleotides of the invention have uses that include, but are not limited to, serving as probes or primers in chromosome identification, chromosome mapping, and linkage analysis.

[159] It has been discovered that this gene is expressed in dendritic cells, T cells, activated T cells, T cell lymphoma, and Hodgkin's lymphoma.

[160] Polynucleotides, translation products and antibodies corresponding to this gene are useful as reagents for differential identification of immune system tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases and/or disorders involving immune system activation, stimulation and/or surveillance, particularly involving T cells, in addition to other immune system cells such as dendritic cells, neutrophils, and leukocytes. Similarly, polypeptides and antibodies

directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). Particularly contemplated are the use of antibodies directed against the extracellular portion of this protein which act as antagonists for the activity of the B7-H11 protein. Such antagonistic antibodies would be useful for the prevention and/or inhibition of such biological activities as are disclosed herein (e.g. T cell modulated activities).

[161] For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

[162] The tissue distribution in immune cells (e.g., T-cells, dendritic cells), and the homology to members of the B7 family of ligands, indicates that the polynucleotides, translation products and antibodies corresponding to this gene are useful for the diagnosis, detection and/or treatment of diseases and/or disorders involving immune system activation, stimulation and/or surveillance, particularly as relating to T cells, neutrophils, dendritic cells, leukocytes, and other immune system cells. In particular, the translation product of the B7-H11 gene may be involved in the costimulation of T cells, binding to ICOS, and/or may play a role in modulation of the expression of particular cytokines, for example.

[163] More generally, the tissue distribution in immune system cells indicates that this gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of immune system origin, polynucleotides, translation products and antibodies corresponding to this gene may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

[164] Polynucleotides, translation products and antibodies corresponding to this gene may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood

lineages, and in the differentiation and/or proliferation of various cell types. Additionally, polynucleotides, translation products and antibodies corresponding to this gene may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement.

FEATURES OF PROTEIN ENCODED BY GENE NO: 5

[165] For purposes of this application, this gene and its corresponding translation product are known as the B7-H10 gene and B7-H10 protein. This protein is believed to reside as a cell-surface molecule, and the transmembrane domain of this protein is believed to approximately embody the following preferred amino acid residues: GPTGARLTLVLALTVILELT (SEQ ID NO: 42). Polynucleotides encoding these polypeptides are also encompassed by the invention, as are antibodies that bind one or more of these polypeptides. Moreover, fragments and variants of these polypeptides (e.g., fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof) are encompassed by the invention. Antibodies that bind these fragments and variants of the invention are also encompassed by the invention. Polynucleotides encoding these fragments and variants are also encompassed by the invention. As one skilled in the art would understand, the transmembrane domain was predicted using computer analysis, and the transmembrane domain may vary by one, two, three, four, five, six, seven, eight, nine, and/or ten amino acids from the N and C-termini of the predicted transmembrane domain.

[166] The B7-H10 gene shares sequence homology with members of the B7 family of ligands. These proteins and their corresponding receptors play vital roles in the growth, differentiation, activation, proliferation and death of T cells. For example, some members of this family (i.e., B7-H1) are involved in costimulation of the T cell response, as well as inducing increased cytokine production, while other family members are involved in the negative regulation of the T cell response. Therefore, agonists and antagonists such as

antibodies or small molecules directed against the B7-H10 gene are useful for treating T cell mediated immune system disorders.

[167] Preferred polypeptides of the present invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, or all seven of the immunogenic epitopes of the extracellular portion of the B7-H10 protein shown in SEQ ID NO: 18 as residues: Glu-34 to Asp-41, Ser-56 to Tyr-61, Pro-152 to Phe-159, Asp-166 to Lys-174, Ala-181 to Asp-200, Tyr-232 to Gly-244, and Pro-381 to Ser-393. Polynucleotides encoding these polypeptides are also encompassed by the invention, as are antibodies that bind one or more of these polypeptides. Moreover, fragments and variants of these polypeptides (e.g., fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof) are encompassed by the invention. Antibodies that bind these fragments and variants of the invention are also encompassed by the invention. Polynucleotides encoding these fragments and variants are also encompassed by the invention.

[168] In additional nonexclusive embodiments, polypeptides of the invention comprises, or alternatively consists of, the following amino acid sequence:

[169] The extracellular domain of the B7-H10 protein: MREIVWYRVTDGGTIKQKIFTFDAMFSTNYSHMENYRKREDLVYQSTVRLPEVRISD NGPYECHVGIYDRATREKVVLASGNIFLNVMAPPTSIEVVAADTPAPFSRYQAQNFT LVCIVSGGKPAPMVYFKRDGEPIDAVPLSEPPAASSGPLQDSRPFRSLLHRDLDDTKM QKSLSLLDAENRGGRPYTERPSRGLTPDPNILLQPTTENIPETVVSREFPRWVHSAEPT YFLRHSRTPSSDGTVEVRALLTWTLNPQIDNEALFSCEVKHPALSMPMQAEVTLVAP KGPKIVMTPSRARVGDTVRILVHGFQNEVFPEPMFTWTRVGSRLLDGSAEFDGKELV LERVPAELNGSMYRCTAQNPLGSTDTHTRLIVFENPNIPRGTEDSNGSI (SEQ ID NO: 43). Polynucleotides encoding these polypeptides are also encompassed by the invention, as are antibodies that bind one or more of these polypeptides. Moreover, fragments and variants of these polypeptides (e.g., fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof) are encompassed by the invention.

Antibodies that bind these fragments and variants of the invention are also encompassed by the invention. Polynucleotides encoding these fragments and variants are also encompassed by the invention.

[170] Also preferred are polypeptides comprising, or alternatively consisting of, fragments of the extracellular portion of the B7-H10 protein demonstrating functional activity (SEQ ID NO: 43). Fragments and/or variants of these polypeptides, such as, for example, fragments and/or variants as described herein, are encompassed by the invention. Polynucleotides encoding these polypeptides (including fragments and/or variants) are also encompassed by the invention, as are antibodies that bind these polypeptides.

[171] By functional activity is meant, a polypeptide fragment capable of displaying one or more known functional activities associated with the full-length (complete) B7-H10 protein. Such functional activities include, but are not limited to, biological activity (e.g., T cell costimulatory activity, ability to bind ICOS, CD28 or CTLA4, and ability to induce or inhibit cytokine production), antigenicity [ability to bind (or compete with a B7-H10 polypeptide for binding) to an anti-B7-H10 antibody], immunogenicity (ability to generate antibody which binds to a B7-H10 polypeptide), ability to form multimers with B7-H10 polypeptides of the invention, and ability to bind to a receptor for a B7-H10 polypeptide.

[172] Figures 9A-B show the nucleotide (SEQ ID NO: 6) and deduced amino acid sequence (SEQ ID NO: 18) corresponding to this gene. Figure 10 shows an analysis of the amino acid sequence (SEQ ID NO: 18). Alpha, beta, turn and coil regions; hydrophilicity and hydrophobicity; amphipathic regions; flexible regions; antigenic index and surface probability are shown, and all were generated using the default settings of the recited computer algorithyms. In the "Antigenic Index or Jameson-Wolf" graph, the positive peaks indicate locations of the highly antigenic regions of the protein, i.e., regions from which epitope-bearing peptides of the invention can be obtained. Polypeptides comprising, or alternatively consisting of, domains defined by these graphs are contemplated by the present invention, as are polynucleotides encoding these polypeptides. The data presented in Figure 10 are also represented in tabular form in Table 7. The columns are labeled with the headings "Res", "Position", and Roman Numerals I-XIV. The column headings refer to the following features of the amino acid sequence presented in Figure 10, and Table 7: "Res": amino acid residue of SEQ ID NO: 18 and Figures 9A-B; "Position": position of the corresponding residue within SEQ ID NO: 18 and Figures 9A-B; I: Alpha, Regions - Garnier-Robson; II:

Alpha, Regions - Chou-Fasman; III: Beta, Regions - Garnier-Robson; IV: Beta, Regions - Chou-Fasman; V: Turn, Regions - Garnier-Robson; VI: Turn, Regions - Chou-Fasman; VII: Coil, Regions - Garnier-Robson; VIII: Hydrophilicity Plot - Kyte-Doolittle; IX: Hydrophobicity Plot - Hopp-Woods; X: Alpha, Amphipathic Regions - Eisenberg; XI: Beta, Amphipathic Regions - Eisenberg; XII: Flexible Regions - Karplus-Schulz; XIII: Antigenic Index - Jameson-Wolf; and XIV: Surface Probability Plot - Emini. Preferred embodiments of the invention in this regard include fragments that comprise, or alternatively consisting of, one or more of the following regions: alpha-helix and alpha-helix forming regions ("alpha-regions"), beta-sheet and beta-sheet forming regions ("beta-regions"), turn and turn-forming regions ("turn-regions"), coil and coil-forming regions ("coil-regions"), hydrophilic regions, hydrophobic regions, alpha amphipathic regions, beta amphipathic regions, flexible regions, surface-forming regions and high antigenic index regions. The data representing the structural or functional attributes of the protein set forth in Figure 10 and/or Table 7, as described above, was generated using the various modules and algorithms of the DNA*STAR set on default parameters. In a preferred embodiment, the data presented in columns VIII, IX, XIII, and XIV of Table 7 can be used to determine regions of the protein which exhibit a high degree of potential for antigenicity. Regions of high antigenicity are determined from the data presented in columns VIII, IX, XIII, and/or XIV by choosing values which represent regions of the polypeptide which are likely to be exposed on the surface of the polypeptide in an environment in which antigen recognition may occur in the process of initiation of an immune response. Certain preferred regions in these regards are set out in Figure 10, but may, as shown in Table 7, be represented or identified by using tabular representations of the data presented in Figure 10. The DNA*STAR computer algorithm used to generate Figure 10 (set on the original default parameters) was used to present the data in Figure 10 in a tabular format (See Table 7). The tabular format of the data in Figure 10 (See Table 7) is used to easily determine specific boundaries of a preferred region.

[173] The present invention is further directed to fragments of the polynucleotide sequences described herein. By a fragment of, for example, the polynucleotide sequence of a deposited cDNA or the nucleotide sequence shown in SEQ ID NO: 6, is intended polynucleotide fragments at least about 15nt, and more preferably at least about 20 nt, at least about 25nt, still more preferably at least about 30 nt, at least about 35nt, and even more preferably, at least about 40 nt in length, at least about 45nt in length, at least about 50nt in

length, at least about 60nt in length, at least about 70nt in length, at least about 80nt in length, at least about 90nt in length, at least about 100nt in length, at least about 125nt in length, at least about 150nt in length, at least about 175nt in length, which are useful as diagnostic probes and primers as discussed herein. Of course, larger fragments 200-1500 nt in length are also useful according to the present invention, as are fragments corresponding to most, if not all, of the nucleotide sequence of a deposited cDNA or as shown in SEQ ID NO: 6. By a fragment at least 20 nt in length, for example, is intended fragments which include 20 or more contiguous bases from the nucleotide sequence of a deposited cDNA or the nucleotide sequence as shown in SEQ ID NO: 6. In this context "about" includes the particularly recited size, an sizes larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Representative examples of polynucleotide fragments of the invention include, for example, fragments that comprise, or alternatively, consist of, a sequence from about nucleotide 1 to about 50, from about 51 to about 100, from about 101 to about 150, from about 151 to about 200, from about 201 to about 250, from about 251 to about 300, from about 301 to about 350, from about 351 to about 400, from about 401 to about 450, from about 451 to about 500, and from about 501 to about 550, and from about 551 to about 600, from about 601 to about 650, from about 651 to about 700, from about 701 to about 750, from about 751 to about 800, and from about 801 to about 860, of SEQ ID NO: 6, or the complementary strand thereto, or the cDNA contained in a deposited clone. In this context "about" includes the particularly recited ranges, and ranges larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. In additional embodiments, the polynucleotides of the invention encode functional attributes of the corresponding protein.

[174] Preferred polypeptide fragments of the invention comprise, or alternatively consist of, the secreted protein having a continuous series of deleted residues from the amino or the carboxy terminus, or both. Particularly, N-terminal deletions of the polypeptide can be described by the general formula m-414 where m is an integer from 2 to 409, where m corresponds to the position of the amino acid residue identified in SEQ ID NO: 18. More in particular, the invention provides polynucleotides encoding polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group: R-2 to T-414; E-3 to T-414; I-4 to T-414; V-5 to T-414; W-6 to T-414; Y-7 to T-414; R-8 to T-414; V-9 to T-414; T-10 to T-414; D-11 to T-414; G-12 to T-414; G-13 to T-414; T-14 to T-414; I-15 to T-414; K-16 to T-414; Q-17 to T-414; K-18 to T-414; I-19 to T-414; F-20 to T-414; T-21 to T-

414; F-22 to T-414; D-23 to T-414; A-24 to T-414; M-25 to T-414; F-26 to T-414; S-27 to T-414; T-28 to T-414; N-29 to T-414; Y-30 to T-414; S-31 to T-414; H-32 to T-414; M-33 to T-414; E-34 to T-414; N-35 to T-414; Y-36 to T-414; R-37 to T-414; K-38 to T-414; R-39 to T-414; E-40 to T-414; D-41 to T-414; L-42 to T-414; V-43 to T-414; Y-44 to T-414; Q-45 to T-414; S-46 to T-414; T-47 to T-414; V-48 to T-414; R-49 to T-414; L-50 to T-414; P-51 to T-414; E-52 to T-414; V-53 to T-414; R-54 to T-414; I-55 to T-414; S-56 to T-414; D-57 to T-414; N-58 to T-414; G-59 to T-414; P-60 to T-414; Y-61 to T-414; E-62 to T-414; C-63 to T-414; H-64 to T-414; V-65 to T-414; G-66 to T-414; I-67 to T-414; Y-68 to T-414; D-69 to T-414; R-70 to T-414; A-71 to T-414; T-72 to T-414; R-73 to T-414; E-74 to T-414; K-75 to T-414; V-76 to T-414; V-77 to T-414; L-78 to T-414; A-79 to T-414; S-80 to T-414; G-81 to T-414; N-82 to T-414; I-83 to T-414; F-84 to T-414; L-85 to T-414; N-86 to T-414; V-87 to T-414; M-88 to T-414; A-89 to T-414; P-90 to T-414; P-91 to T-414; T-92 to T-414; S-93 to T-414; I-94 to T-414; E-95 to T-414; V-96 to T-414; V-97 to T-414; A-98 to T-414; A-99 to T-414; D-100 to T-414; T-101 to T-414; P-102 to T-414; A-103 to T-414; P-104 to T-414; F-105 to T-414; S-106 to T-414; R-107 to T-414; Y-108 to T-414; Q-109 to T-414; A-110 to T-414; Q-111 to T-414; N-112 to T-414; F-113 to T-414; T-114 to T-414; L-115 to T-414; V-116 to T-414; C-117 to T-414; I-118 to T-414; V-119 to T-414; S-120 to T-414; G-121 to T-414; G-122 to T-414; K-123 to T-414; P-124 to T-414; A-125 to T-414; P-126 to T-414; M-127 to T-414; V-128 to T-414; Y-129 to T-414; F-130 to T-414; K-131 to T-414; R-132 to T-414; D-133 to T-414; G-134 to T-414; E-135 to T-414; P-136 to T-414; I-137 to T-414; D-138 to T-414; A-139 to T-414; V-140 to T-414; P-141 to T-414; L-142 to T-414; S-143 to T-414; E-144 to T-414; P-145 to T-414; P-146 to T-414; A-147 to T-414; A-148 to T-414; S-149 to T-414; S-150 to T-414; G-151 to T-414; P-152 to T-414; L-153 to T-414; Q-154 to T-414; D-155 to T-414; S-156 to T-414; R-157 to T-414; P-158 to T-414; F-159 to T-414; R-160 to T-414; S-161 to T-414; L-162 to T-414; L-163 to T-414; H-164 to T-414; R-165 to T-414; D-166 to T-414; L-167 to T-414; D-168 to T-414; D-169 to T-414; T-170 to T-414; K-171 to T-414; M-172 to T-414; Q-173 to T-414; K-174 to T-414; S-175 to T-414; L-176 to T-414; S-177 to T-414; L-178 to T-414; L-179 to T-414; D-180 to T-414; A-181 to T-414; E-182 to T-414; N-183 to T-414; R-184 to T-414; G-185 to T-414; G-186 to T-414; R-187 to T-414; P-188 to T-414; Y-189 to T-414; T-190 to T-414; E-191 to T-414; R-192 to T-414; P-193 to T-414; S-194 to T-414; R-195 to T-414; G-196 to T-414; L-197 to T-414; T-198 to T-414; P-199 to T-414; D-200 to T-414; P-201 to T-414; N-202 to T-414; I-203 to T-414; L-

204 to T-414; L-205 to T-414; Q-206 to T-414; P-207 to T-414; T-208 to T-414; T-209 to T-414; E-210 to T-414; N-211 to T-414; I-212 to T-414; P-213 to T-414; E-214 to T-414; T-215 to T-414; V-216 to T-414; V-217 to T-414; S-218 to T-414; R-219 to T-414; E-220 to T-414; F-221 to T-414; P-222 to T-414; R-223 to T-414; W-224 to T-414; V-225 to T-414; H-226 to T-414; S-227 to T-414; A-228 to T-414; E-229 to T-414; P-230 to T-414; T-231 to T-414; Y-232 to T-414; F-233 to T-414; L-234 to T-414; R-235 to T-414; H-236 to T-414; S-237 to T-414; R-238 to T-414; T-239 to T-414; P-240 to T-414; S-241 to T-414; S-242 to T-414; D-243 to T-414; G-244 to T-414; T-245 to T-414; V-246 to T-414; E-247 to T-414; V-248 to T-414; R-249 to T-414; A-250 to T-414; L-251 to T-414; L-252 to T-414; T-253 to T-414; W-254 to T-414; T-255 to T-414; L-256 to T-414; N-257 to T-414; P-258 to T-414; Q-259 to T-414; I-260 to T-414; D-261 to T-414; N-262 to T-414; E-263 to T-414; A-264 to T-414; L-265 to T-414; F-266 to T-414; S-267 to T-414; C-268 to T-414; E-269 to T-414; V-270 to T-414; K-271 to T-414; H-272 to T-414; P-273 to T-414; A-274 to T-414; L-275 to T-414; S-276 to T-414; M-277 to T-414; P-278 to T-414; M-279 to T-414; Q-280 to T-414; A-281 to T-414; E-282 to T-414; V-283 to T-414; T-284 to T-414; L-285 to T-414; V-286 to T-414; A-287 to T-414; P-288 to T-414; K-289 to T-414; G-290 to T-414; P-291 to T-414; K-292 to T-414; I-293 to T-414; V-294 to T-414; M-295 to T-414; T-296 to T-414; P-297 to T-414; S-298 to T-414; R-299 to T-414; A-300 to T-414; R-301 to T-414; V-302 to T-414; G-303 to T-414; D-304 to T-414; T-305 to T-414; V-306 to T-414; R-307 to T-414; I-308 to T-414; L-309 to T-414; V-310 to T-414; H-311 to T-414; G-312 to T-414; F-313 to T-414; Q-314 to T-414; N-315 to T-414; E-316 to T-414; V-317 to T-414; F-318 to T-414; P-319 to T-414; E-320 to T-414; P-321 to T-414; M-322 to T-414; F-323 to T-414; T-324 to T-414; W-325 to T-414; T-326 to T-414; R-327 to T-414; V-328 to T-414; G-329 to T-414; S-330 to T-414; R-331 to T-414; L-332 to T-414; L-333 to T-414; D-334 to T-414; G-335 to T-414; S-336 to T-414; A-337 to T-414; E-338 to T-414; F-339 to T-414; D-340 to T-414; G-341 to T-414; K-342 to T-414; E-343 to T-414; L-344 to T-414; V-345 to T-414; L-346 to T-414; E-347 to T-414; R-348 to T-414; V-349 to T-414; P-350 to T-414; A-351 to T-414; E-352 to T-414; L-353 to T-414; N-354 to T-414; G-355 to T-414; S-356 to T-414; M-357 to T-414; Y-358 to T-414; R-359 to T-414; C-360 to T-414; T-361 to T-414; A-362 to T-414; Q-363 to T-414; N-364 to T-414; P-365 to T-414; L-366 to T-414; G-367 to T-414; S-368 to T-414; T-369 to T-414; D-370 to T-414; T-371 to T-414; H-372 to T-414; T-373 to T-414; R-374 to T-414; L-375 to T-414; I-376 to T-414; V-377 to T-414; F-378 to T-414; E-379 to T-414; N-

380 to T-414; P-381 to T-414; N-382 to T-414; I-383 to T-414; P-384 to T-414; R-385 to T-414; G-386 to T-414; T-387 to T-414; E-388 to T-414; D-389 to T-414; S-390 to T-414; N-391 to T-414; G-392 to T-414; S-393 to T-414; I-394 to T-414; G-395 to T-414; P-396 to T-414; T-397 to T-414; G-398 to T-414; A-399 to T-414; R-400 to T-414; L-401 to T-414; T-402 to T-414; L-403 to T-414; V-404 to T-414; L-405 to T-414; A-406 to T-414; L-407 to T-414; T-408 to T-414; and/or V-409 to T-414 of SEQ ID NO: 18. Polynucleotides encoding these polypeptides are also encompassed by the invention, as are antibodies that bind one or more of these polypeptides. Moreover, fragments and variants of these polypeptides (e.g., fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof) are encompassed by the invention. Antibodies that bind these fragments and variants of the invention are also encompassed by the invention. Polynucleotides encoding these fragments and variants are also encompassed by the invention.

[175] Accordingly, the present invention further provides polypeptides having one or more residues deleted from the carboxy terminus of the amino acid sequence of the polypeptide shown in Figures 9A-B (SEQ ID NO: 18), as described by the general formula 1-n, where n is an integer from 7 to 413, where n corresponds to the position of the amino acid residue identified in SEQ ID NO: 18. Additionally, the invention provides polynucleotides encoding polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the following group of C-terminal deletions: M-1 to L-413; M-1 to E-412; M-1 to L-411; M-1 to I-410; M-1 to V-409; M-1 to T-408; M-1 to L-407; M-1 to A-406; M-1 to L-405; M-1 to V-404; M-1 to L-403; M-1 to T-402; M-1 to L-401; M-1 to R-400; M-1 to A-399; M-1 to G-398; M-1 to T-397; M-1 to P-396; M-1 to G-395; M-1 to I-394; M-1 to S-393; M-1 to G-392; M-1 to N-391; M-1 to S-390; M-1 to D-389; M-1 to E-388; M-1 to T-387; M-1 to G-386; M-1 to R-385; M-1 to P-384; M-1 to I-383; M-1 to N-382; M-1 to P-381; M-1 to N-380; M-1 to E-379; M-1 to F-378; M-1 to V-377; M-1 to I-376; M-1 to L-375; M-1 to R-374; M-1 to T-373; M-1 to H-372; M-1 to T-371; M-1 to D-370; M-1 to T-369; M-1 to S-368; M-1 to G-367; M-1 to L-366; M-1 to P-365; M-1 to N-364; M-1 to Q-363; M-1 to A-362; M-1 to T-361; M-1 to C-360; M-1 to R-359; M-1 to Y-358; M-1 to M-357; M-1 to S-356; M-1 to G-355; M-1 to N-354; M-1 to L-353; M-1 to E-352; M-1 to A-351; M-1 to P-

350; M-1 to V-349; M-1 to R-348; M-1 to E-347; M-1 to L-346; M-1 to V-345; M-1 to L-344; M-1 to E-343; M-1 to K-342; M-1 to G-341; M-1 to D-340; M-1 to F-339; M-1 to E-338; M-1 to A-337; M-1 to S-336; M-1 to G-335; M-1 to D-334; M-1 to L-333; M-1 to L-332; M-1 to R-331; M-1 to S-330; M-1 to G-329; M-1 to V-328; M-1 to R-327; M-1 to T-326; M-1 to W-325; M-1 to T-324; M-1 to F-323; M-1 to M-322; M-1 to P-321; M-1 to E-320; M-1 to P-319; M-1 to F-318; M-1 to V-317; M-1 to E-316; M-1 to N-315; M-1 to Q-314; M-1 to F-313; M-1 to G-312; M-1 to H-311; M-1 to V-310; M-1 to L-309; M-1 to I-308; M-1 to R-307; M-1 to V-306; M-1 to T-305; M-1 to D-304; M-1 to G-303; M-1 to V-302; M-1 to R-301; M-1 to A-300; M-1 to R-299; M-1 to S-298; M-1 to P-297; M-1 to T-296; M-1 to M-295; M-1 to V-294; M-1 to I-293; M-1 to K-292; M-1 to P-291; M-1 to G-290; M-1 to K-289; M-1 to P-288; M-1 to A-287; M-1 to V-286; M-1 to L-285; M-1 to T-284; M-1 to V-283; M-1 to E-282; M-1 to A-281; M-1 to Q-280; M-1 to M-279; M-1 to P-278; M-1 to M-277; M-1 to S-276; M-1 to L-275; M-1 to A-274; M-1 to P-273; M-1 to H-272; M-1 to K-271; M-1 to V-270; M-1 to E-269; M-1 to C-268; M-1 to S-267; M-1 to F-266; M-1 to L-265; M-1 to A-264; M-1 to E-263; M-1 to N-262; M-1 to D-261; M-1 to I-260; M-1 to Q-259; M-1 to P-258; M-1 to N-257; M-1 to L-256; M-1 to T-255; M-1 to W-254; M-1 to T-253; M-1 to L-252; M-1 to L-251; M-1 to A-250; M-1 to R-249; M-1 to V-248; M-1 to E-247; M-1 to V-246; M-1 to T-245; M-1 to G-244; M-1 to D-243; M-1 to S-242; M-1 to S-241; M-1 to P-240; M-1 to T-239; M-1 to R-238; M-1 to S-237; M-1 to H-236; M-1 to R-235; M-1 to L-234; M-1 to F-233; M-1 to Y-232; M-1 to T-231; M-1 to P-230; M-1 to E-229; M-1 to A-228; M-1 to S-227; M-1 to H-226; M-1 to V-225; M-1 to W-224; M-1 to R-223; M-1 to P-222; M-1 to F-221; M-1 to E-220; M-1 to R-219; M-1 to S-218; M-1 to V-217; M-1 to V-216; M-1 to T-215; M-1 to E-214; M-1 to P-213; M-1 to I-212; M-1 to N-211; M-1 to E-210; M-1 to T-209; M-1 to T-208; M-1 to P-207; M-1 to Q-206; M-1 to L-205; M-1 to L-204; M-1 to I-203; M-1 to N-202; M-1 to P-201; M-1 to D-200; M-1 to P-199; M-1 to T-198; M-1 to L-197; M-1 to G-196; M-1 to R-195; M-1 to S-194; M-1 to P-193; M-1 to R-192; M-1 to E-191; M-1 to T-190; M-1 to Y-189; M-1 to P-188; M-1 to R-187; M-1 to G-186; M-1 to G-185; M-1 to R-184; M-1 to N-183; M-1 to E-182; M-1 to A-181; M-1 to D-180; M-1 to L-179; M-1 to L-178; M-1 to S-177; M-1 to L-176; M-1 to S-175; M-1 to K-174; M-1 to Q-173; M-1 to M-172; M-1 to K-171; M-1 to T-170; M-1 to D-169; M-1 to D-168; M-1 to L-167; M-1 to D-166; M-1 to R-165; M-1 to H-164; M-1 to L-163; M-1 to L-162; M-1 to S-161; M-1 to R-160; M-1 to F-159; M-1 to P-158; M-1 to R-157; M-1 to S-156; M-1 to D-

155; M-1 to Q-154; M-1 to L-153; M-1 to P-152; M-1 to G-151; M-1 to S-150; M-1 to S-149; M-1 to A-148; M-1 to A-147; M-1 to P-146; M-1 to P-145; M-1 to E-144; M-1 to S-143; M-1 to L-142; M-1 to P-141; M-1 to V-140; M-1 to A-139; M-1 to D-138; M-1 to I-137; M-1 to P-136; M-1 to E-135; M-1 to G-134; M-1 to D-133; M-1 to R-132; M-1 to K-131; M-1 to F-130; M-1 to Y-129; M-1 to V-128; M-1 to M-127; M-1 to P-126; M-1 to A-125; M-1 to P-124; M-1 to K-123; M-1 to G-122; M-1 to G-121; M-1 to S-120; M-1 to V-119; M-1 to I-118; M-1 to C-117; M-1 to V-116; M-1 to L-115; M-1 to T-114; M-1 to F-113; M-1 to N-112; M-1 to Q-111; M-1 to A-110; M-1 to Q-109; M-1 to Y-108; M-1 to R-107; M-1 to S-106; M-1 to F-105; M-1 to P-104; M-1 to A-103; M-1 to P-102; M-1 to T-101; M-1 to D-100; M-1 to A-99; M-1 to A-98; M-1 to V-97; M-1 to V-96; M-1 to E-95; M-1 to I-94; M-1 to S-93; M-1 to T-92; M-1 to P-91; M-1 to P-90; M-1 to A-89; M-1 to M-88; M-1 to V-87; M-1 to N-86; M-1 to L-85; M-1 to F-84; M-1 to I-83; M-1 to N-82; M-1 to G-81; M-1 to S-80; M-1 to A-79; M-1 to L-78; M-1 to V-77; M-1 to V-76; M-1 to K-75; M-1 to E-74; M-1 to R-73; M-1 to T-72; M-1 to A-71; M-1 to R-70; M-1 to D-69; M-1 to Y-68; M-1 to I-67; M-1 to G-66; M-1 to V-65; M-1 to H-64; M-1 to C-63; M-1 to E-62; M-1 to Y-61; M-1 to P-60; M-1 to G-59; M-1 to N-58; M-1 to D-57; M-1 to S-56; M-1 to I-55; M-1 to R-54; M-1 to V-53; M-1 to E-52; M-1 to P-51; M-1 to L-50; M-1 to R-49; M-1 to V-48; M-1 to T-47; M-1 to S-46; M-1 to Q-45; M-1 to Y-44; M-1 to V-43; M-1 to L-42; M-1 to D-41; M-1 to E-40; M-1 to R-39; M-1 to K-38; M-1 to R-37; M-1 to Y-36; M-1 to N-35; M-1 to E-34; M-1 to M-33; M-1 to H-32; M-1 to S-31; M-1 to Y-30; M-1 to N-29; M-1 to T-28; M-1 to S-27; M-1 to F-26; M-1 to M-25; M-1 to A-24; M-1 to D-23; M-1 to F-22; M-1 to T-21; M-1 to F-20; M-1 to I-19; M-1 to K-18; M-1 to Q-17; M-1 to K-16; M-1 to I-15; M-1 to T-14; M-1 to G-13; M-1 to G-12; M-1 to D-11; M-1 to T-10; M-1 to V-9; M-1 to R-8; and/or M-1 to Y-7 of SEQ ID NO: 18. Polynucleotides encoding these polypeptides are also encompassed by the invention, as are antibodies that bind one or more of these polypeptides. Moreover, fragments and variants of these polypeptides (e.g., fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof) are encompassed by the invention. Antibodies that bind these fragments and variants of the invention are also encompassed by the invention. Polynucleotides encoding these fragments and variants are also encompassed by the invention.

[176] Also as mentioned above, even if deletion of one or more amino acids from the C-terminus of a protein results in modification of loss of one or more biological functions of the protein (e.g., ability to inhibit the Mixed Lymphocyte Reaction), other functional activities (e.g., biological activities, ability to multimerize, ability to bind receptor, ability to generate antibodies, ability to bind antibodies) may still be retained. For example, the ability of the shortened polypeptide to induce and/or bind to antibodies which recognize the complete or mature forms of the polypeptide generally will be retained when less than the majority of the residues of the complete or mature polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a polypeptide with a large number of deleted C-terminal amino acid residues may retain some biological or immunogenic activities. In fact, peptides composed of as few as six amino acid residues may often evoke an immune response.

[177] In addition, any of the above listed N- or C-terminal deletions can be combined to produce a N- and C-terminal deleted polypeptide. The invention also provides polypeptides comprising, or alternatively consisting of, one or more amino acids deleted from both the amino and the carboxyl termini, which may be described generally as having residues m-n of SEQ ID NO: 18, where n and m are integers as described above. Polynucleotides encoding these polypeptides are also encompassed by the invention. The present invention is also directed to proteins containing polypeptides at least 80%, 85%, 90%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to a polypeptide sequence set forth herein as m-n. In preferred embodiments, the application is directed to proteins containing polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to polypeptides having the amino acid sequence of the specific N- and C-terminal deletions recited herein. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[178] Also included are polynucleotide sequences encoding a polypeptide consisting of a portion of the complete amino acid sequence encoded by a cDNA clone contained in ATCC Deposit No. PTA-2332, where this portion excludes any integer of amino acid residues from 1 to about 408 amino acids from the amino terminus of the complete amino acid sequence encoded by a cDNA clone contained in ATCC Deposit No. PTA-2332, or any integer of amino acid residues from 1 to about 408 amino acids from the carboxy terminus, or any

combination of the above amino terminal and carboxy terminal deletions, of the complete amino acid sequence encoded by the cDNA clone contained in ATCC Deposit No. PTA-2332. Polypeptides encoded by these polynucleotides also are encompassed by the invention.

[179] As described herein or otherwise known in the art, the polynucleotides of the invention have uses that include, but are not limited to, serving as probes or primers in chromosome identification, chromosome mapping, and linkage analysis.

[180] It has been discovered that this gene is expressed in neural tissues.

[181] Polynucleotides and polypeptides of the invention are useful as reagents for differential identification of neural system tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases and/or disorders involving immune system activation, stimulation and/or surveillance, particularly involving T cells and/or neutrophils, as well as diseases and/or disorders of the neural system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). Particularly contemplated are the use of antibodies directed against the extracellular portion of this protein which act as antagonists for the activity of the B7-H10 protein. Such antagonistic antibodies would be useful for the prevention and/or inhibition of such biological activites as are disclosed herein (e.g., T cell modulated activities).

[182] For a number of disorders of the above tissues or cells, particularly of the neural and immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, neural, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

[183] The homology to members of the B7 family of ligands, indicates that the polynucleotides and polypeptides corresponding to this gene are useful for the diagnosis, detection and/or treatment of diseases and/or disorders involving immune system activation, stimulation and/or surveillance, particularly as relating to T cells and/or neutrophils. In particular, the translation product of the B7-H10 gene may be involved in the costimulation

of T cells, binding to ICOS, and/or may play a role in modulation of the expression of particular cytokines, for example.

[184] More generally, the tissue distribution in immune system cells indicates that this gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of immune system origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement.

[185] Expression within neural tissue suggests that polynucleotides, translation products and antibodies corresponding to this clone are useful for the detection and/or treatment of neurodegenerative disease states and behavioural disorders such as Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders. Additionally, translation products corresponding to this gene, as well as antibodies directed against these translation products, may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

FEATURES OF PROTEIN ENCODED BY GENE NO: 6

[186] For purposes of this application, this gene and its corresponding translation product are known as the B7-H12 gene and B7-H12 protein. The B7-H12 gene shares sequence homology with members of the B7 family of ligands (i.e., B7-H1 (See Genbank Accession AAF25807)). These proteins and their corresponding receptors play vital roles in the growth, differentiation, activation, proliferation and death of T cells. For example, some members of this family (i.e., B7-H1) are involved in costimulation of the T cell response, as well as inducing increased cytokine production, while other family members are involved in the negative regulation of the T cell response. Therefore, agonists and antagonists such as antibodies or small molecules directed against the B7-H12 gene are useful for treating T cell mediated immune system disorders, as well as disorders of other immune system cells, such as for example, neutrophils, macrophage, and leukocytes.

[187] Preferred polypeptides of the present invention comprise, or alternatively consist of, one, two, three, four, or all four of the immunogenic epitopes of the extracellular portion of the B7-H12 protein shown in SEQ ID NO: 19 as residues: Pro-54 to Glu-59, Lys-78 to Arg-94, Ala-115 to Ile-120, and Gln-126 to Cys-131. Polynucleotides encoding these polypeptides are also encompassed by the invention, as are antibodies that bind one or more of these polypeptides. Moreover, fragments and variants of these polypeptides (e.g., fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof) are encompassed by the invention. Antibodies that bind these fragments and variants of the invention are also encompassed by the invention. Polynucleotides encoding these fragments and variants are also encompassed by the invention.

[188] In additional nonexclusive embodiments, polypeptides of the invention comprise, or alternatively consist of, an amino acid sequence selected from the group consisting of:

[189] The mature domain of the B7-H12 protein: QVTVVGPTDPILAMVGENTTLRCCLSPEENAEDMEVRWFQSQFSPAVFVYKGGRER TEEQKEEYRGRTTFVSKDSRGSVALIIHNVTAEDNGIYQCYFQEGRSCNEAILHLVVA DQHNPLSWIPIPQGTLSL (SEQ ID NO: 44) and/or

[190] The leader sequence of the B7-H12 protein: MEPAAALHFSRPASLLLLLSLCALVSA (SEQ ID NO: 45). Polynucleotides encoding

these polypeptides are also encompassed by the invention, as are antibodies that bind one or more of these polypeptides. Moreover, fragments and variants of these polypeptides (e.g., fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof) are encompassed by the invention. Antibodies that bind these fragments and variants of the invention are also encompassed by the invention. Polynucleotides encoding these fragments and variants are also encompassed by the invention.

[191] Also preferred are polypeptides comprising, or alternatively consisting of, fragments of the mature portion of the B7-H12 protein demonstrating functional activity (SEQ ID NO: 44). Fragments and/or variants of these polypeptides, such as, for example, fragments and/or variants as described herein, are encompassed by the invention. Polynucleotides encoding these polypeptides (including fragments and/or variants) are also encompassed by the invention, as are antibodies that bind these polypeptides.

[192] By functional activity is meant, a polypeptide fragment capable of displaying one or more known functional activities associated with the full-length (complete) B7-H12 protein. Such functional activities include, but are not limited to, biological activity (e.g., T cell costimulatory activity, ability to bind ICOS, CD28 or CTLA4, and ability to induce or inhibit cytokine production), antigenicity [ability to bind (or compete with a B7-H12 polypeptide for binding) to an anti-B7-H12 antibody], immunogenicity (ability to generate antibody which binds to a B7-H12 polypeptide), ability to form multimers with B7-H12 polypeptides of the invention, and ability to bind to a receptor for a B7-H12 polypeptide.

[193] Figures 11A-B show the nucleotide (SEQ ID NO: 7) and deduced amino acid sequence (SEQ ID NO: 19) corresponding to this gene.

[194] Figure 12 shows an analysis of the amino acid sequence (SEQ ID NO: 19). Alpha, beta, turn and coil regions; hydrophilicity and hydrophobicity; amphipathic regions; flexible regions; antigenic index and surface probability are shown, and all were generated using the default settings of the recited computer algorithyms. In the "Antigenic Index or Jameson-Wolf" graph, the positive peaks indicate locations of the highly antigenic regions of the protein, i.e., regions from which epitope-bearing peptides of the invention can be obtained. Polypeptides comprising, or alternatively consisting of, domains defined by these graphs are

contemplated by the present invention, as are polynucleotides encoding these polypeptides. The data presented in Figure 12 are also represented in tabular form in Table 8. The columns are labeled with the headings "Res", "Position", and Roman Numerals I-XIV. The column headings refer to the following features of the amino acid sequence presented in Figure 12, and Table 8: "Res": amino acid residue of SEQ ID NO: 19 and Figures 11A-B; "Position": position of the corresponding residue within SEQ ID NO: 19 and Figures 11A-B; I: Alpha, Regions - Garnier-Robson; II: Alpha, Regions - Chou-Fasman; III: Beta, Regions - Garnier-Robson; IV: Beta, Regions - Chou-Fasman; V: Turn, Regions - Garnier-Robson; VI: Turn, Regions - Chou-Fasman; VII: Coil, Regions - Garnier-Robson; VIII: Hydrophilicity Plot - Kyte-Doolittle; IX: Hydrophobicity Plot - Hopp-Woods; X: Alpha, Amphipathic Regions - Eisenberg; XI: Beta, Amphipathic Regions - Eisenberg; XII: Flexible Regions - Karplus-Schulz; XIII: Antigenic Index - Jameson-Wolf; and XIV: Surface Probability Plot - Emini. Preferred embodiments of the invention in this regard include fragments that comprise, or alternatively consisting of, one or more of the following regions: alpha-helix and alpha-helix forming regions ("alpha-regions"), beta-sheet and beta-sheet forming regions ("beta-regions"), turn and turn-forming regions ("turn-regions"), coil and coil-forming regions ("coil-regions"), hydrophilic regions, hydrophobic regions, alpha amphipathic regions, beta amphipathic regions, flexible regions, surface-forming regions and high antigenic index regions. The data representing the structural or functional attributes of the protein set forth in Figure 12 and/or Table 8, as described above, was generated using the various modules and algorithms of the DNA*STAR set on default parameters. In a preferred embodiment, the data presented in columns VIII, IX, XIII, and XIV of Table 8 can be used to determine regions of the protein which exhibit a high degree of potential for antigenicity. Regions of high antigenicity are determined from the data presented in columns VIII, IX, XIII, and/or XIV by choosing values which represent regions of the polypeptide which are likely to be exposed on the surface of the polypeptide in an environment in which antigen recognition may occur in the process of initiation of an immune response. Certain preferred regions in these regards are set out in Figure 12, but may, as shown in Table 8, be represented or identified by using tabular representations of the data presented in Figure 12. The DNA*STAR computer algorithm used to generate Figure 12 (set on the original default parameters) was used to present the data in Figure 12 in a tabular format (See Table 8). The tabular format of the data

in Figure 12 (See Figure 8) is used to easily determine specific boundaries of a preferred region.

[195] The present invention is further directed to fragments of the polynucleotide sequences described herein. By a fragment of, for example, the polynucleotide sequence of a deposited cDNA or the nucleotide sequence shown in SEQ ID NO: 7, is intended polynucleotide fragments at least about 15nt, and more preferably at least about 20 nt, at least about 25nt, still more preferably at least about 30 nt, at least about 35nt, and even more preferably, at least about 40 nt in length, at least about 45nt in length, at least about 50nt in length, at least about 60nt in length, at least about 70nt in length, at least about 80nt in length, at least about 90nt in length, at least about 100nt in length, at least about 125nt in length, at least about 150nt in length, at least about 175nt in length, which are useful as diagnostic probes and primers as discussed herein. Of course, larger fragments 200-1500 nt in length are also useful according to the present invention, as are fragments corresponding to most, if not all, of the nucleotide sequence of a deposited cDNA or as shown in SEQ ID NO: 7. By a fragment at least 20 nt in length, for example, is intended fragments which include 20 or more contiguous bases from the nucleotide sequence of a deposited cDNA or the nucleotide sequence as shown in SEQ ID NO: 7. In this context "about" includes the particularly recited size, an sizes larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Representative examples of polynucleotide fragments of the invention include, for example, fragments that comprise, or alternatively, consist of, a sequence from about nucleotide 1 to about 50, from about 51 to about 100, from about 101 to about 150, from about 151 to about 200, from about 201 to about 250, from about 251 to about 300, from about 301 to about 350, from about 351 to about 400, from about 401 to about 450, from about 451 to about 500, and from about 501 to about 550, and from about 551 to about 600, from about 601 to about 650, from about 651 to about 700, from about 701 to about 750, from about 751 to about 800, and from about 801 to about 860, of SEQ ID NO: 7, or the complementary strand thereto, or the cDNA contained in a deposited clone. In this context "about" includes the particularly recited ranges, and ranges larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. In additional embodiments, the polynucleotides of the invention encode functional attributes of the corresponding protein.

[196] Preferred polypeptide fragments of the invention comprise, or alternatively consist of, the secreted protein having a continuous series of deleted residues from the amino or the carboxy terminus, or both. Particularly, N-terminal deletions of the B7-H12 polypeptide can be described by the general formula m-159 where m is an integer from 2 to 154, where m corresponds to the position of the amino acid residue identified in SEQ ID NO: 19. More in particular, the invention provides polynucleotides encoding polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group: E-2 to L-159; P-3 to L-159; A-4 to L-159; A-5 to L-159; A-6 to L-159; L-7 to L-159; H-8 to L-159; F-9 to L-159; S-10 to L-159; R-11 to L-159; P-12 to L-159; A-13 to L-159; S-14 to L-159; L-15 to L-159; L-16 to L-159; L-17 to L-159; L-18 to L-159; L-19 to L-159; S-20 to L-159; L-21 to L-159; C-22 to L-159; A-23 to L-159; L-24 to L-159; V-25 to L-159; S-26 to L-159; A-27 to L-159; Q-28 to L-159; V-29 to L-159; T-30 to L-159; V-31 to L-159; V-32 to L-159; G-33 to L-159; P-34 to L-159; T-35 to L-159; D-36 to L-159; P-37 to L-159; I-38 to L-159; L-39 to L-159; A-40 to L-159; M-41 to L-159; V-42 to L-159; G-43 to L-159; E-44 to L-159; N-45 to L-159; T-46 to L-159; T-47 to L-159; L-48 to L-159; R-49 to L-159; C-50 to L-159; C-51 to L-159; L-52 to L-159; S-53 to L-159; P-54 to L-159; E-55 to L-159; E-56 to L-159; N-57 to L-159; A-58 to L-159; E-59 to L-159; D-60 to L-159; M-61 to L-159; E-62 to L-159; V-63 to L-159; R-64 to L-159; W-65 to L-159; F-66 to L-159; Q-67 to L-159; S-68 to L-159; Q-69 to L-159; F-70 to L-159; S-71 to L-159; P-72 to L-159; A-73 to L-159; V-74 to L-159; F-75 to L-159; V-76 to L-159; Y-77 to L-159; K-78 to L-159; G-79 to L-159; G-80 to L-159; R-81 to L-159; E-82 to L-159; R-83 to L-159; T-84 to L-159; E-85 to L-159; E-86 to L-159; Q-87 to L-159; K-88 to L-159; E-89 to L-159; E-90 to L-159; Y-91 to L-159; R-92 to L-159; G-93 to L-159; R-94 to L-159; T-95 to L-159; T-96 to L-159; F-97 to L-159; V-98 to L-159; S-99 to L-159; K-100 to L-159; D-101 to L-159; S-102 to L-159; R-103 to L-159; G-104 to L-159; S-105 to L-159; V-106 to L-159; A-107 to L-159; L-108 to L-159; I-109 to L-159; I-110 to L-159; H-111 to L-159; N-112 to L-159; V-113 to L-159; T-114 to L-159; A-115 to L-159; E-116 to L-159; D-117 to L-159; N-118 to L-159; G-119 to L-159; I-120 to L-159; Y-121 to L-159; Q-122 to L-159; C-123 to L-159; Y-124 to L-159; F-125 to L-159; Q-126 to L-159; E-127 to L-159; G-128 to L-159; R-129 to L-159; S-130 to L-159; C-131 to L-159; N-132 to L-159; E-133 to L-159; A-134 to L-159; I-135 to L-159; L-136 to L-159; H-137 to L-159; L-138 to L-159; V-139 to L-159; V-140 to L-159; A-141 to L-159; D-142 to L-159; Q-143 to L-159; H-144 to L-159; N-145 to L-159; P-146 to L-159; L-147 to L-159; S-148 to L-159;

W-149 to L-159; I-150 to L-159; P-151 to L-159; I-152 to L-159; P-153 to L-159; and/or Q-154 to L-159 of SEQ ID NO: 19. Polynucleotides encoding these polypeptides are also encompassed by the invention, as are antibodies that bind one or more of these polypeptides. Moreover, fragments and variants of these polypeptides (e.g., fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof) are encompassed by the invention. Antibodies that bind these fragments and variants of the invention are also encompassed by the invention. Polynucleotides encoding these fragments and variants are also encompassed by the invention.

[197] Accordingly, the present invention further provides polypeptides having one or more residues deleted from the carboxy terminus of the amino acid sequence of the polypeptide shown in Figures 11A-B (SEQ ID NO: 19), as described by the general formula 1-n, where n is an integer from 7 to 158, where n corresponds to the position of the amino acid residue identified in SEQ ID NO: 19. Additionally, the invention provides polynucleotides encoding polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the following group of C-terminal deletions: M-1 to S-158; M-1 to L-157; M-1 to T-156; M-1 to G-155; M-1 to Q-154; M-1 to P-153; M-1 to I-152; M-1 to P-151; M-1 to I-150; M-1 to W-149; M-1 to S-148; M-1 to L-147; M-1 to P-146; M-1 to N-145; M-1 to H-144; M-1 to Q-143; M-1 to D-142; M-1 to A-141; M-1 to V-140; M-1 to V-139; M-1 to L-138; M-1 to H-137; M-1 to L-136; M-1 to I-135; M-1 to A-134; M-1 to E-133; M-1 to N-132; M-1 to C-131; M-1 to S-130; M-1 to R-129; M-1 to G-128; M-1 to E-127; M-1 to Q-126; M-1 to F-125; M-1 to Y-124; M-1 to C-123; M-1 to Q-122; M-1 to Y-121; M-1 to I-120; M-1 to G-119; M-1 to N-118; M-1 to D-117; M-1 to E-116; M-1 to A-115; M-1 to T-114; M-1 to V-113; M-1 to N-112; M-1 to H-111; M-1 to I-110; M-1 to I-109; M-1 to L-108; M-1 to A-107; M-1 to V-106; M-1 to S-105; M-1 to G-104; M-1 to R-103; M-1 to S-102; M-1 to D-101; M-1 to K-100; M-1 to S-99; M-1 to V-98; M-1 to F-97; M-1 to T-96; M-1 to T-95; M-1 to R-94; M-1 to G-93; M-1 to R-92; M-1 to Y-91; M-1 to E-90; M-1 to E-89; M-1 to K-88; M-1 to Q-87; M-1 to E-86; M-1 to E-85; M-1 to T-84; M-1 to R-83; M-1 to E-82; M-1 to R-81; M-1 to G-80; M-1 to G-79; M-1 to K-78; M-1 to Y-77; M-1 to V-76; M-1 to F-75; M-1 to V-74; M-1 to A-73; M-1 to P-72; M-1 to S-71; M-1 to F-70; M-1 to Q-69; M-1 to S-68; M-1 to Q-67; M-1 to F-66; M-1 to W-65; M-1 to R-64; M-1 to V-63; M-1 to E-

62; M-1 to M-61; M-1 to D-60; M-1 to E-59; M-1 to A-58; M-1 to N-57; M-1 to E-56; M-1 to E-55; M-1 to P-54; M-1 to S-53; M-1 to L-52; M-1 to C-51; M-1 to C-50; M-1 to R-49; M-1 to L-48; M-1 to T-47; M-1 to T-46; M-1 to N-45; M-1 to E-44; M-1 to G-43; M-1 to V-42; M-1 to M-41; M-1 to A-40; M-1 to L-39; M-1 to I-38; M-1 to P-37; M-1 to D-36; M-1 to T-35; M-1 to P-34; M-1 to G-33; M-1 to V-32; M-1 to V-31; M-1 to T-30; M-1 to V-29; M-1 to Q-28; M-1 to A-27; M-1 to S-26; M-1 to V-25; M-1 to L-24; M-1 to A-23; M-1 to C-22; M-1 to L-21; M-1 to S-20; M-1 to L-19; M-1 to L-18; M-1 to L-17; M-1 to L-16; M-1 to L-15; M-1 to S-14; M-1 to A-13; M-1 to P-12; M-1 to R-11; M-1 to S-10; M-1 to F-9; M-1 to H-8; and/or M-1 to L-7 of SEQ ID NO: 19. Polynucleotides encoding these polypeptides are also encompassed by the invention, as are antibodies that bind one or more of these polypeptides. Moreover, fragments and variants of these polypeptides (e.g., fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof) are encompassed by the invention. Antibodies that bind these fragments and variants of the invention are also encompassed by the invention. Polynucleotides encoding these fragments and variants are also encompassed by the invention.

[198] Also as mentioned above, even if deletion of one or more amino acids from the C-terminus of a protein results in modification of loss of one or more biological functions of the protein (e.g., ability to inhibit the Mixed Lymphocyte Reaction), other functional activities (e.g., biological activities, ability to multimerize, ability to bind receptor, ability to generate antibodies, ability to bind antibodies) may still be retained. For example, the ability of the shortened polypeptide to induce and/or bind to antibodies which recognize the complete or mature forms of the polypeptide generally will be retained when less than the majority of the residues of the complete or mature polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a polypeptide with a large number of deleted C-terminal amino acid residues may retain some biological or immunogenic activities. In fact, peptides composed of as few as six amino acid residues may often evoke an immune response.

[199] In addition, any of the above listed N- or C-terminal deletions can be combined to produce a N- and C-terminal deleted polypeptide. The invention also provides polypeptides comprising, or alternatively consisting of, one or more amino acids deleted from both the amino and the carboxyl termini, which may be described generally as having residues m-n of SEQ ID NO: 19, where n and m are integers as described above. Fragments and/or variants of these polypeptides, such as, for example, fragments and/or variants as described herein, are encompassed by the invention. Polynucleotides encoding these polypeptides (including fragments and/or variants) are also encompassed by the invention, as are antibodies that bind these polypeptides.

[200] The present invention is also directed to proteins containing polypeptides at least 80%, 85%, 90%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to a polypeptide sequence set forth herein as m-n. In preferred embodiments, the application is directed to proteins containing polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to polypeptides having the amino acid sequence of the specific N- and C-terminal deletions recited herein. Fragments and/or variants of these polypeptides, such as, for example, fragments and/or variants as described herein, are encompassed by the invention. Polynucleotides encoding these polypeptides (including fragments and/or variants) are also encompassed by the invention, as are antibodies that bind these polypeptides.

[201] Also included are polynucleotide sequences encoding a polypeptide consisting of a portion of the complete amino acid sequence encoded by a cDNA clone contained in ATCC Deposit No. PTA-2332, where this portion excludes any integer of amino acid residues from 1 to about 153 amino acids from the amino terminus of the complete amino acid sequence encoded by a cDNA clone contained in ATCC Deposit No. PTA-2332, or any integer of amino acid residues from 1 to about 153 amino acids from the carboxy terminus, or any combination of the above amino terminal and carboxy terminal deletions, of the complete amino acid sequence encoded by the cDNA clone contained in ATCC Deposit No. PTA-2332. Polypeptides encoded by these polynucleotides also are encompassed by the invention.

[202] As described herein or otherwise known in the art, the polynucleotides of the invention have uses that include, but are not limited to, serving as probes or primers in chromosome identification, chromosome mapping, and linkage analysis.

[203] It has been discovered that this gene is expressed in dendritic cells, T cells, and Hodgkin's lymphoma.

[204] Polynucleotides, translation products and antibodies corresponding to this gene are useful as reagents for differential identification of immune system tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases and/or disorders involving immune system activation, stimulation and/or surveillance, particularly involving T cells, in addition to other immune system cells such as dendritic cells, neutrophils, and leukocytes. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). Particularly contemplated are the use of antibodies directed against the extracellular portion of this protein which act as antagonists for the activity of the B7-H12 protein. Such antagonistic antibodies would be useful for the prevention and/or inhibition of such biological activites as are disclosed herein (e.g. T cell modulated activities).

[205] For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

[206] The tissue distribution in immune cells (e.g., T-cells, dendritic cells), and the homology to members of the B7 family of ligands, indicates that the polynucleotides, translation products and antibodies corresponding to this gene are useful for the diagnosis, detection and/or treatment of diseases and/or disorders involving immune system activation, stimulation and/or surveillance, particularly as relating to T cells, neutrophils, dendritic cells, leukocytes, and other immune system cells. In particular, the translation product of the B7-H12 gene may be involved in the costimulation of T cells, binding to ICOS, and/or may play a role in modulation of the expression of particular cytokines, for example.

[207] More generally, the tissue distribution in immune system cells indicates that this gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g., by boosting immune responses). Since the gene is expressed in cells of immune system origin,

polynucleotides, translation products and antibodies corresponding to this gene may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

[208] Polynucleotides, translation products and antibodies corresponding to this gene may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement.

FEATURES OF PROTEIN ENCODED BY GENE NO: 7

[209] For purposes of this application, this gene and its corresponding translation product are known as the B7-H13 gene and B7-H13 protein. This protein is believed to reside as a cell-surface molecule, and the transmembrane domain of this protein is believed to approximately embody the following preferred amino acid residues: LGILCCGLFFGIV (SEQ ID NO: 46). Polynucleotides encoding these polypeptides are also encompassed by the invention, as are antibodies that bind one or more of these polypeptides. Moreover, fragments and variants of these polypeptides (e.g., fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof) are encompassed by the invention. Antibodies that bind these fragments and variants of the invention are also encompassed by the invention. Polynucleotides encoding these fragments and variants are also encompassed by the invention. As one skilled in the art would understand, the transmembrane domain was predicted using computer analysis, and the transmembrane domain may vary by one, two, three, four, five, six, seven, eight, nine, and/or ten amino acids from the N and C-termini of the predicted transmembrane domain.

[210] The B7-H13 gene shares sequence homology with members of the B7 family of ligands (i.e., B7-H1 (See Genbank Accession AAF25807)). These proteins and their corresponding receptors play vital roles in the growth, differentiation, activation, proliferation

and death of T cells. For example, some members of this family (i.e., B7-H1) are involved in costimulation of the T cell response, as well as inducing increased cytokine production, while other family members are involved in the negative regulation of the T cell response. Therefore, agonists and antagonists such as antibodies or small molecules directed against the B7-H13 gene are useful for treating T cell mediated immune system disorders, as well as disorders of other immune system cells, such as for example, neutrophils, macrophage, and leukocytes.

[211] Preferred polypeptides of the present invention comprise, or alternatively consist of, one, two, three, four, five, six, seven, or all seven of the immunogenic epitopes of the extracellular portion of the B7-H13 protein shown in SEQ ID NO: 20 as residues: Tyr-67 to Pro-74, Ser-117 to Gln-123, Pro-161 to Met-185, His-311 to Arg-327, Val-345 to Trp-353, Arg-359 to Glu-367, and Pro-447 to Gln-461. Polynucleotides encoding these polypeptides are also encompassed by the invention, as are antibodies that bind one or more of these polypeptides. Moreover, fragments and variants of these polypeptides (e.g., fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof) are encompassed by the invention. Antibodies that bind these fragments and variants of the invention are also encompassed by the invention. Polynucleotides encoding these fragments and variants are also encompassed by the invention.

[212] In additional nonexclusive embodiments, polypeptides of the invention comprise, or alternatively consist of, an amino acid sequence selected from the group consisting of:

[213] The extracellular domain of the B7-H13 protein: MALMLSLVLSLLKLGSGQWQVFGPDKPVQALVGEDAAFSCFLSPKTNAEAMEVRFF RGQFSSVVHLYRDGKDQPFMQMPQYQGRTKLVKDSIAEGRISLRLENITVLDAGLYG CRISSQSYYQKAIWELQVSALGSVPLISITGYVDRDIQLLCQSSGWFPRPTAKWKGPQ GQDLSTDSRTNRDMHGLFDVEISLTVQENAGSISCSMRHAHLSREVESRVQIGDTFFE PISWHLATKV (SEQ ID NO: 48),

[214] The mature extracellular domain of the B7-H13 protein: QWQVFGPDKPVQALVGEDAAFSCFLSPKTNAEAMEVRFFRGQFSSVVHLYRDGKD QPFMQMPQYQGRTKLVKDSIAEGRISLRLENITVLDAGLYGCRISSQSYYQKAIWEL

QVSALGSVPLISITGYVDRDIQLLCQSSGWFPRPTAKWKGPQGQDLSTDSRTNRDMH GLFDVEISLTVQENAGSISCSMRHAHLSREVESRVQIGDTFFEPISWHLATKV (SEQ ID NO: 49), and/or

[215] The leader sequence of the B7-H13 protein: MALMLSLVLSLLKLGSG (SEQ ID NO: 47). Polynucleotides encoding these polypeptides are also encompassed by the invention, as are antibodies that bind one or more of these polypeptides. Moreover, fragments and variants of these polypeptides (e.g., fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof) are encompassed by the invention. Antibodies that bind these fragments and variants of the invention are also encompassed by the invention. Polynucleotides encoding these fragments and variants are also encompassed by the invention.

[216] Also preferred are polypeptides comprising, or alternatively consisting of, fragments of the mature extracellular portion of the B7-H13 protein demonstrating functional activity (SEQ ID NO: 49). Fragments and/or variants of these polypeptides, such as, for example, fragments and/or variants as described herein, are encompassed by the invention. Polynucleotides encoding these polypeptides (including fragments and/or variants) are also encompassed by the invention, as are antibodies that bind these polypeptides.

[217] By functional activity is meant, a polypeptide fragment capable of displaying one or more known functional activities associated with the full-length (complete) B7-H13 protein. Such functional activities include, but are not limited to, biological activity (e.g., T cell costimulatory activity, ability to bind ICOS, CD28 or CTLA4, and ability to induce or inhibit cytokine production), antigenicity [ability to bind (or compete with a B7-H13 polypeptide for binding) to an anti-B7-H13 antibody], immunogenicity (ability to generate antibody which binds to a B7-H13 polypeptide), ability to form multimers with B7-H13 polypeptides of the invention, and ability to bind to a receptor for a B7-H13 polypeptide.

[218] Figures 13A-C show the nucleotide (SEQ ID NO: 8) and deduced amino acid sequence (SEQ ID NO: 20) corresponding to this gene.

[219] Figure 14 shows an analysis of the amino acid sequence (SEQ ID NO: 20). Alpha, beta, turn and coil regions; hydrophilicity and hydrophobicity; amphipathic regions; flexible regions; antigenic index and surface probability are shown, and all were generated using the

default settings of the recited computer algorithyms. In the "Antigenic Index or Jameson-Wolf" graph, the positive peaks indicate locations of the highly antigenic regions of the protein, i.e., regions from which epitope-bearing peptides of the invention can be obtained. Polypeptides comprising, or alternatively consisting of, domains defined by these graphs are contemplated by the present invention, as are polynucleotides encoding these polypeptides. The data presented in Figure 14 are also represented in tabular form in Table 9. The columns are labeled with the headings "Res", "Position", and Roman Numerals I-XIV. The column headings refer to the following features of the amino acid sequence presented in Figure 14, and Table 9: "Res": amino acid residue of SEQ ID NO: 20 and Figures 13A-C; "Position": position of the corresponding residue within SEQ ID NO: 20 and Figures 13A-C; I: Alpha, Regions - Garnier-Robson; II: Alpha, Regions - Chou-Fasman; III: Beta, Regions - Garnier-Robson; IV: Beta, Regions - Chou-Fasman; V: Turn, Regions - Garnier-Robson; VI: Turn, Regions - Chou-Fasman; VII: Coil, Regions - Garnier-Robson; VIII: Hydrophilicity Plot - Kyte-Doolittle; IX: Hydrophobicity Plot - Hopp-Woods; X: Alpha, Amphipathic Regions - Eisenberg; XI: Beta, Amphipathic Regions - Eisenberg; XII: Flexible Regions - Karplus-Schulz; XIII: Antigenic Index - Jameson-Wolf; and XIV: Surface Probability Plot - Emini. Preferred embodiments of the invention in this regard include fragments that comprise, or alternatively consisting of, one or more of the following regions: alpha-helix and alpha-helix forming regions ("alpha-regions"), beta-sheet and beta-sheet forming regions ("beta-regions"), turn and turn-forming regions ("turn-regions"), coil and coil-forming regions ("coil-regions"), hydrophilic regions, hydrophobic regions, alpha amphipathic regions, beta amphipathic regions, flexible regions, surface-forming regions and high antigenic index regions. The data representing the structural or functional attributes of the protein set forth in Figure 14 and/or Table 9, as described above, was generated using the various modules and algorithms of the DNA*STAR set on default parameters. In a preferred embodiment, the data presented in columns VIII, IX, XIII, and XIV of Table 9 can be used to determine regions of the protein which exhibit a high degree of potential for antigenicity. Regions of high antigenicity are determined from the data presented in columns VIII, IX, XIII, and/or XIV by choosing values which represent regions of the polypeptide which are likely to be exposed on the surface of the polypeptide in an environment in which antigen recognition may occur in the process of initiation of an immune response. Certain preferred regions in these regards are set out in Figure 14, but may, as shown in Table 9, be represented or identified by using

tabular representations of the data presented in Figure 14. The DNA*STAR computer algorithm used to generate Figure 14 (set on the original default parameters) was used to present the data in Figure 14 in a tabular format (See Table 9). The tabular format of the data in Figure 14 (See Table 9) is used to easily determine specific boundaries of a preferred region.

[220] The present invention is further directed to fragments of the polynucleotide sequences described herein. By a fragment of, for example, the polynucleotide sequence of a deposited cDNA or the nucleotide sequence shown in SEQ ID NO: 8, is intended polynucleotide fragments at least about 15nt, and more preferably at least about 20 nt, at least about 25nt, still more preferably at least about 30 nt, at least about 35nt, and even more preferably, at least about 40 nt in length, at least about 45nt in length, at least about 50nt in length, at least about 60nt in length, at least about 70nt in length, at least about 80nt in length, at least about 90nt in length, at least about 100nt in length, at least about 125nt in length, at least about 150nt in length, at least about 175nt in length, which are useful as diagnostic probes and primers as discussed herein. Of course, larger fragments 200-1500 nt in length are also useful according to the present invention, as are fragments corresponding to most, if not all, of the nucleotide sequence of a deposited cDNA or as shown in SEQ ID NO: 8. By a fragment at least 20 nt in length, for example, is intended fragments which include 20 or more contiguous bases from the nucleotide sequence of a deposited cDNA or the nucleotide sequence as shown in SEQ ID NO: 8. In this context "about" includes the particularly recited size, an sizes larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Representative examples of polynucleotide fragments of the invention include, for example, fragments that comprise, or alternatively, consist of, a sequence from about nucleotide 1 to about 50, from about 51 to about 100, from about 101 to about 150, from about 151 to about 200, from about 201 to about 250, from about 251 to about 300, from about 301 to about 350, from about 351 to about 400, from about 401 to about 450, from about 451 to about 500, and from about 501 to about 550, and from about 551 to about 600, from about 601 to about 650, from about 651 to about 700, from about 701 to about 750, from about 751 to about 800, and from about 801 to about 860, of SEQ ID NO: 8, or the complementary strand thereto, or the cDNA contained in a deposited clone. In this context "about" includes the particularly recited ranges, and ranges larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini.

[221] In additional embodiments, the polynucleotides of the invention encode functional attributes of the corresponding protein. Preferred polypeptide fragments of the invention comprise, or alternatively consist of, the secreted protein having a continuous series of deleted residues from the amino or the carboxy terminus, or both. Particularly, N-terminal deletions of the polypeptide can be described by the general formula m-461 where m is an integer from 2 to 456, where m corresponds to the position of the amino acid residue identified in SEQ ID NO: 20. More in particular, the invention provides polynucleotides encoding polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group: A-2 to Q-461; L-3 to Q-461; M-4 to Q-461; L-5 to Q-461; S-6 to Q-461; L-7 to Q-461; V-8 to Q-461; L-9 to Q-461; S-10 to Q-461; L-11 to Q-461; L-12 to Q-461; K-13 to Q-461; L-14 to Q-461; G-15 to Q-461; S-16 to Q-461; G-17 to Q-461; Q-18 to Q-461; W-19 to Q-461; Q-20 to Q-461; V-21 to Q-461; F-22 to Q-461; G-23 to Q-461; P-24 to Q-461; D-25 to Q-461; K-26 to Q-461; P-27 to Q-461; V-28 to Q-461; Q-29 to Q-461; A-30 to Q-461; L-31 to Q-461; V-32 to Q-461; G-33 to Q-461; E-34 to Q-461; D-35 to Q-461; A-36 to Q-461; A-37 to Q-461; F-38 to Q-461; S-39 to Q-461; C-40 to Q-461; F-41 to Q-461; L-42 to Q-461; S-43 to Q-461; P-44 to Q-461; K-45 to Q-461; T-46 to Q-461; N-47 to Q-461; A-48 to Q-461; E-49 to Q-461; A-50 to Q-461; M-51 to Q-461; E-52 to Q-461; V-53 to Q-461; R-54 to Q-461; F-55 to Q-461; F-56 to Q-461; R-57 to Q-461; G-58 to Q-461; Q-59 to Q-461; F-60 to Q-461; S-61 to Q-461; S-62 to Q-461; V-63 to Q-461; V-64 to Q-461; H-65 to Q-461; L-66 to Q-461; Y-67 to Q-461; R-68 to Q-461; D-69 to Q-461; G-70 to Q-461; K-71 to Q-461; D-72 to Q-461; Q-73 to Q-461; P-74 to Q-461; F-75 to Q-461; M-76 to Q-461; Q-77 to Q-461; M-78 to Q-461; P-79 to Q-461; Q-80 to Q-461; Y-81 to Q-461; Q-82 to Q-461; G-83 to Q-461; R-84 to Q-461; T-85 to Q-461; K-86 to Q-461; L-87 to Q-461; V-88 to Q-461; K-89 to Q-461; D-90 to Q-461; S-91 to Q-461; I-92 to Q-461; A-93 to Q-461; E-94 to Q-461; G-95 to Q-461; R-96 to Q-461; I-97 to Q-461; S-98 to Q-461; L-99 to Q-461; R-100 to Q-461; L-101 to Q-461; E-102 to Q-461; N-103 to Q-461; I-104 to Q-461; T-105 to Q-461; V-106 to Q-461; L-107 to Q-461; D-108 to Q-461; A-109 to Q-461; G-110 to Q-461; L-111 to Q-461; Y-112 to Q-461; G-113 to Q-461; C-114 to Q-461; R-115 to Q-461; I-116 to Q-461; S-117 to Q-461; S-118 to Q-461; Q-119 to Q-461; S-120 to Q-461; Y-121 to Q-461; Y-122 to Q-461; Q-123 to Q-461; K-124 to Q-461; A-125 to Q-461; I-126 to Q-461; W-127 to Q-461; E-128 to Q-461; L-129 to Q-461; Q-130 to Q-461; V-131 to Q-461; S-132 to Q-461; A-133 to Q-461; L-134 to Q-461; G-135 to Q-461; S-136 to Q-461; V-137 to Q-461; P-

138 to Q-461; L-139 to Q-461; I-140 to Q-461; S-141 to Q-461; I-142 to Q-461; T-143 to Q-461; G-144 to Q-461; Y-145 to Q-461; V-146 to Q-461; D-147 to Q-461; R-148 to Q-461; D-149 to Q-461; I-150 to Q-461; Q-151 to Q-461; L-152 to Q-461; L-153 to Q-461; C-154 to Q-461; Q-155 to Q-461; S-156 to Q-461; S-157 to Q-461; G-158 to Q-461; W-159 to Q-461; F-160 to Q-461; P-161 to Q-461; R-162 to Q-461; P-163 to Q-461; T-164 to Q-461; A-165 to Q-461; K-166 to Q-461; W-167 to Q-461; K-168 to Q-461; G-169 to Q-461; P-170 to Q-461; Q-171 to Q-461; G-172 to Q-461; Q-173 to Q-461; D-174 to Q-461; L-175 to Q-461; S-176 to Q-461; T-177 to Q-461; D-178 to Q-461; S-179 to Q-461; R-180 to Q-461; T-181 to Q-461; N-182 to Q-461; R-183 to Q-461; D-184 to Q-461; M-185 to Q-461; H-186 to Q-461; G-187 to Q-461; L-188 to Q-461; F-189 to Q-461; D-190 to Q-461; V-191 to Q-461; E-192 to Q-461; I-193 to Q-461; S-194 to Q-461; L-195 to Q-461; T-196 to Q-461; V-197 to Q-461; Q-198 to Q-461; E-199 to Q-461; N-200 to Q-461; A-201 to Q-461; G-202 to Q-461; S-203 to Q-461; I-204 to Q-461; S-205 to Q-461; C-206 to Q-461; S-207 to Q-461; M-208 to Q-461; R-209 to Q-461; H-210 to Q-461; A-211 to Q-461; H-212 to Q-461; L-213 to Q-461; S-214 to Q-461; R-215 to Q-461; E-216 to Q-461; V-217 to Q-461; E-218 to Q-461; S-219 to Q-461; R-220 to Q-461; V-221 to Q-461; Q-222 to Q-461; I-223 to Q-461; G-224 to Q-461; D-225 to Q-461; T-226 to Q-461; F-227 to Q-461; F-228 to Q-461; E-229 to Q-461; P-230 to Q-461; I-231 to Q-461; S-232 to Q-461; W-233 to Q-461; H-234 to Q-461; L-235 to Q-461; A-236 to Q-461; T-237 to Q-461; K-238 to Q-461; V-239 to Q-461; L-240 to Q-461; G-241 to Q-461; I-242 to Q-461; L-243 to Q-461; C-244 to Q-461; C-245 to Q-461; G-246 to Q-461; L-247 to Q-461; F-248 to Q-461; F-249 to Q-461; G-250 to Q-461; I-251 to Q-461; V-252 to Q-461; G-253 to Q-461; L-254 to Q-461; K-255 to Q-461; I-256 to Q-461; F-257 to Q-461; F-258 to Q-461; S-259 to Q-461; K-260 to Q-461; F-261 to Q-461; Q-262 to Q-461; W-263 to Q-461; K-264 to Q-461; I-265 to Q-461; Q-266 to Q-461; A-267 to Q-461; E-268 to Q-461; L-269 to Q-461; D-270 to Q-461; W-271 to Q-461; R-272 to Q-461; R-273 to Q-461; K-274 to Q-461; H-275 to Q-461; G-276 to Q-461; Q-277 to Q-461; A-278 to Q-461; E-279 to Q-461; L-280 to Q-461; R-281 to Q-461; D-282 to Q-461; A-283 to Q-461; R-284 to Q-461; K-285 to Q-461; H-286 to Q-461; A-287 to Q-461; V-288 to Q-461; E-289 to Q-461; V-290 to Q-461; T-291 to Q-461; L-292 to Q-461; D-293 to Q-461; P-294 to Q-461; E-295 to Q-461; T-296 to Q-461; A-297 to Q-461; H-298 to Q-461; P-299 to Q-461; K-300 to Q-461; L-301 to Q-461; C-302 to Q-461; V-303 to Q-461; S-304 to Q-461; D-305 to Q-461; L-306 to Q-461; K-307 to Q-461; T-308 to Q-461; V-309 to Q-461; T-310 to Q-461; H-311 to

Q-461; R-312 to Q-461; K-313 to Q-461; A-314 to Q-461; P-315 to Q-461; Q-316 to Q-461; E-317 to Q-461; V-318 to Q-461; P-319 to Q-461; H-320 to Q-461; S-321 to Q-461; E-322 to Q-461; K-323 to Q-461; R-324 to Q-461; F-325 to Q-461; T-326 to Q-461; R-327 to Q-461; K-328 to Q-461; S-329 to Q-461; V-330 to Q-461; V-331 to Q-461; A-332 to Q-461; S-333 to Q-461; Q-334 to Q-461; S-335 to Q-461; F-336 to Q-461; Q-337 to Q-461; A-338 to Q-461; G-339 to Q-461; K-340 to Q-461; H-341 to Q-461; Y-342 to Q-461; W-343 to Q-461; E-344 to Q-461; V-345 to Q-461; D-346 to Q-461; G-347 to Q-461; G-348 to Q-461; H-349 to Q-461; N-350 to Q-461; K-351 to Q-461; R-352 to Q-461; W-353 to Q-461; R-354 to Q-461; V-355 to Q-461; G-356 to Q-461; V-357 to Q-461; C-358 to Q-461; R-359 to Q-461; D-360 to Q-461; D-361 to Q-461; V-362 to Q-461; D-363 to Q-461; R-364 to Q-461; R-365 to Q-461; K-366 to Q-461; E-367 to Q-461; Y-368 to Q-461; V-369 to Q-461; T-370 to Q-461; L-371 to Q-461; S-372 to Q-461; P-373 to Q-461; D-374 to Q-461; H-375 to Q-461; G-376 to Q-461; Y-377 to Q-461; W-378 to Q-461; V-379 to Q-461; L-380 to Q-461; R-381 to Q-461; L-382 to Q-461; N-383 to Q-461; G-384 to Q-461; E-385 to Q-461; H-386 to Q-461; L-387 to Q-461; Y-388 to Q-461; F-389 to Q-461; T-390 to Q-461; L-391 to Q-461; N-392 to Q-461; P-393 to Q-461; R-394 to Q-461; F-395 to Q-461; I-396 to Q-461; S-397 to Q-461; V-398 to Q-461; F-399 to Q-461; P-400 to Q-461; R-401 to Q-461; T-402 to Q-461; P-403 to Q-461; P-404 to Q-461; T-405 to Q-461; K-406 to Q-461; I-407 to Q-461; G-408 to Q-461; V-409 to Q-461; F-410 to Q-461; L-411 to Q-461; D-412 to Q-461; Y-413 to Q-461; E-414 to Q-461; C-415 to Q-461; G-416 to Q-461; T-417 to Q-461; I-418 to Q-461; S-419 to Q-461; F-420 to Q-461; F-421 to Q-461; N-422 to Q-461; I-423 to Q-461; N-424 to Q-461; D-425 to Q-461; Q-426 to Q-461; S-427 to Q-461; L-428 to Q-461; I-429 to Q-461; Y-430 to Q-461; T-431 to Q-461; L-432 to Q-461; T-433 to Q-461; C-434 to Q-461; R-435 to Q-461; F-436 to Q-461; E-437 to Q-461; G-438 to Q-461; L-439 to Q-461; L-440 to Q-461; R-441 to Q-461; P-442 to Q-461; Y-443 to Q-461; I-444 to Q-461; E-445 to Q-461; Y-446 to Q-461; P-447 to Q-461; S-448 to Q-461; Y-449 to Q-461; N-450 to Q-461; E-451 to Q-461; Q-452 to Q-461; N-453 to Q-461; G-454 to Q-461; T-455 to Q-461; and/or P-456 to Q-461 of SEQ ID NO: 20. Polynucleotides encoding these polypeptides are also encompassed by the invention, as are antibodies that bind one or more of these polypeptides. Moreover, fragments and variants of these polypeptides (e.g., fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to

the polynucleotide encoding these polypeptides, or the complement thereof) are encompassed by the invention. Antibodies that bind these fragments and variants of the invention are also encompassed by the invention. Polynucleotides encoding these fragments and variants are also encompassed by the invention.

[222] Accordingly, the present invention further provides polypeptides having one or more residues deleted from the carboxy terminus of the amino acid sequence of the polypeptide shown in Figures 13A-C (SEQ ID NO: 20), as described by the general formula 1-n, where n is an integer from 7 to 460, where n corresponds to the position of the amino acid residue identified in SEQ ID NO: 20. Additionally, the invention provides polynucleotides encoding polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the following group of C-terminal deletions: M-1 to Q-460; M-1 to K-459; M-1 to D-458; M-1 to R-457; M-1 to P-456; M-1 to T-455; M-1 to G-454; M-1 to N-453; M-1 to Q-452; M-1 to E-451; M-1 to N-450; M-1 to Y-449; M-1 to S-448; M-1 to P-447; M-1 to Y-446; M-1 to E-445; M-1 to I-444; M-1 to Y-443; M-1 to P-442; M-1 to R-441; M-1 to L-440; M-1 to L-439; M-1 to G-438; M-1 to E-437; M-1 to F-436; M-1 to R-435; M-1 to C-434; M-1 to T-433; M-1 to L-432; M-1 to T-431; M-1 to Y-430; M-1 to I-429; M-1 to L-428; M-1 to S-427; M-1 to Q-426; M-1 to D-425; M-1 to N-424; M-1 to I-423; M-1 to N-422; M-1 to F-421; M-1 to F-420; M-1 to S-419; M-1 to I-418; M-1 to T-417; M-1 to G-416; M-1 to C-415; M-1 to E-414; M-1 to Y-413; M-1 to D-412; M-1 to L-411; M-1 to F-410; M-1 to V-409; M-1 to G-408; M-1 to I-407; M-1 to K-406; M-1 to T-405; M-1 to P-404; M-1 to P-403; M-1 to T-402; M-1 to R-401; M-1 to P-400; M-1 to F-399; M-1 to V-398; M-1 to S-397; M-1 to I-396; M-1 to F-395; M-1 to R-394; M-1 to P-393; M-1 to N-392; M-1 to L-391; M-1 to T-390; M-1 to F-389; M-1 to Y-388; M-1 to L-387; M-1 to H-386; M-1 to E-385; M-1 to G-384; M-1 to N-383; M-1 to L-382; M-1 to R-381; M-1 to L-380; M-1 to V-379; M-1 to W-378; M-1 to Y-377; M-1 to G-376; M-1 to H-375; M-1 to D-374; M-1 to P-373; M-1 to S-372; M-1 to L-371; M-1 to T-370; M-1 to V-369; M-1 to Y-368; M-1 to E-367; M-1 to K-366; M-1 to R-365; M-1 to R-364; M-1 to D-363; M-1 to V-362; M-1 to D-361; M-1 to D-360; M-1 to R-359; M-1 to C-358; M-1 to V-357; M-1 to G-356; M-1 to V-355; M-1 to R-354; M-1 to W-353; M-1 to R-352; M-1 to K-351; M-1 to N-350; M-1 to H-349; M-1 to G-348; M-1 to G-347; M-1 to D-346; M-1 to V-345; M-1 to E-344; M-1 to W-343; M-1 to Y-342; M-1 to H-341; M-1 to K-340; M-1 to G-339; M-1 to A-338; M-1 to Q-337; M-1 to F-336; M-1 to S-335; M-1 to Q-334; M-1 to S-333; M-1 to A-332; M-1 to V-331; M-1 to V-

330; M-1 to S-329; M-1 to K-328; M-1 to R-327; M-1 to T-326; M-1 to F-325; M-1 to R-324; M-1 to K-323; M-1 to E-322; M-1 to S-321; M-1 to H-320; M-1 to P-319; M-1 to V-318; M-1 to E-317; M-1 to Q-316; M-1 to P-315; M-1 to A-314; M-1 to K-313; M-1 to R-312; M-1 to H-311; M-1 to T-310; M-1 to V-309; M-1 to T-308; M-1 to K-307; M-1 to L-306; M-1 to D-305; M-1 to S-304; M-1 to V-303; M-1 to C-302; M-1 to L-301; M-1 to K-300; M-1 to P-299; M-1 to H-298; M-1 to A-297; M-1 to T-296; M-1 to E-295; M-1 to P-294; M-1 to D-293; M-1 to L-292; M-1 to T-291; M-1 to V-290; M-1 to E-289; M-1 to V-288; M-1 to A-287; M-1 to H-286; M-1 to K-285; M-1 to R-284; M-1 to A-283; M-1 to D-282; M-1 to R-281; M-1 to L-280; M-1 to E-279; M-1 to A-278; M-1 to Q-277; M-1 to G-276; M-1 to H-275; M-1 to K-274; M-1 to R-273; M-1 to R-272; M-1 to W-271; M-1 to D-270; M-1 to L-269; M-1 to E-268; M-1 to A-267; M-1 to Q-266; M-1 to I-265; M-1 to K-264; M-1 to W-263; M-1 to Q-262; M-1 to F-261; M-1 to K-260; M-1 to S-259; M-1 to F-258; M-1 to F-257; M-1 to I-256; M-1 to K-255; M-1 to L-254; M-1 to G-253; M-1 to V-252; M-1 to I-251; M-1 to G-250; M-1 to F-249; M-1 to F-248; M-1 to L-247; M-1 to G-246; M-1 to C-245; M-1 to C-244; M-1 to L-243; M-1 to I-242; M-1 to G-241; M-1 to L-240; M-1 to V-239; M-1 to K-238; M-1 to T-237; M-1 to A-236; M-1 to L-235; M-1 to H-234; M-1 to W-233; M-1 to S-232; M-1 to I-231; M-1 to P-230; M-1 to E-229; M-1 to F-228; M-1 to F-227; M-1 to T-226; M-1 to D-225; M-1 to G-224; M-1 to I-223; M-1 to Q-222; M-1 to V-221; M-1 to R-220; M-1 to S-219; M-1 to E-218; M-1 to V-217; M-1 to E-216; M-1 to R-215; M-1 to S-214; M-1 to L-213; M-1 to H-212; M-1 to A-211; M-1 to H-210; M-1 to R-209; M-1 to M-208; M-1 to S-207; M-1 to C-206; M-1 to S-205; M-1 to I-204; M-1 to S-203; M-1 to G-202; M-1 to A-201; M-1 to N-200; M-1 to E-199; M-1 to Q-198; M-1 to V-197; M-1 to T-196; M-1 to L-195; M-1 to S-194; M-1 to I-193; M-1 to E-192; M-1 to V-191; M-1 to D-190; M-1 to F-189; M-1 to L-188; M-1 to G-187; M-1 to H-186; M-1 to M-185; M-1 to D-184; M-1 to R-183; M-1 to N-182; M-1 to T-181; M-1 to R-180; M-1 to S-179; M-1 to D-178; M-1 to T-177; M-1 to S-176; M-1 to L-175; M-1 to D-174; M-1 to Q-173; M-1 to G-172; M-1 to Q-171; M-1 to P-170; M-1 to G-169; M-1 to K-168; M-1 to W-167; M-1 to K-166; M-1 to A-165; M-1 to T-164; M-1 to P-163; M-1 to R-162; M-1 to P-161; M-1 to F-160; M-1 to W-159; M-1 to G-158; M-1 to S-157; M-1 to S-156; M-1 to Q-155; M-1 to C-154; M-1 to L-153; M-1 to L-152; M-1 to Q-151; M-1 to I-150; M-1 to D-149; M-1 to R-148; M-1 to D-147; M-1 to V-146; M-1 to Y-145; M-1 to G-144; M-1 to T-143; M-1 to I-142; M-1 to S-141; M-1 to I-140; M-1 to L-139; M-1 to P-138; M-1 to V-137; M-1 to S-136; M-1 to G-135; M-1

to L-134; M-1 to A-133; M-1 to S-132; M-1 to V-131; M-1 to Q-130; M-1 to L-129; M-1 to E-128; M-1 to W-127; M-1 to I-126; M-1 to A-125; M-1 to K-124; M-1 to Q-123; M-1 to Y-122; M-1 to Y-121; M-1 to S-120; M-1 to Q-119; M-1 to S-118; M-1 to S-117; M-1 to I-116; M-1 to R-115; M-1 to C-114; M-1 to G-113; M-1 to Y-112; M-1 to L-111; M-1 to G-110; M-1 to A-109; M-1 to D-108; M-1 to L-107; M-1 to V-106; M-1 to T-105; M-1 to I-104; M-1 to N-103; M-1 to E-102; M-1 to L-101; M-1 to R-100; M-1 to L-99; M-1 to S-98; M-1 to I-97; M-1 to R-96; M-1 to G-95; M-1 to E-94; M-1 to A-93; M-1 to I-92; M-1 to S-91; M-1 to D-90; M-1 to K-89; M-1 to V-88; M-1 to L-87; M-1 to K-86; M-1 to T-85; M-1 to R-84; M-1 to G-83; M-1 to Q-82; M-1 to Y-81; M-1 to Q-80; M-1 to P-79; M-1 to M-78; M-1 to Q-77; M-1 to M-76; M-1 to F-75; M-1 to P-74; M-1 to Q-73; M-1 to D-72; M-1 to K-71; M-1 to G-70; M-1 to D-69; M-1 to R-68; M-1 to Y-67; M-1 to L-66; M-1 to H-65; M-1 to V-64; M-1 to V-63; M-1 to S-62; M-1 to S-61; M-1 to F-60; M-1 to Q-59; M-1 to G-58; M-1 to R-57; M-1 to F-56; M-1 to F-55; M-1 to R-54; M-1 to V-53; M-1 to E-52; M-1 to M-51; M-1 to A-50; M-1 to E-49; M-1 to A-48; M-1 to N-47; M-1 to T-46; M-1 to K-45; M-1 to P-44; M-1 to S-43; M-1 to L-42; M-1 to F-41; M-1 to C-40; M-1 to S-39; M-1 to F-38; M-1 to A-37; M-1 to A-36; M-1 to D-35; M-1 to E-34; M-1 to G-33; M-1 to V-32; M-1 to L-31; M-1 to A-30; M-1 to Q-29; M-1 to V-28; M-1 to P-27; M-1 to K-26; M-1 to D-25; M-1 to P-24; M-1 to G-23; M-1 to F-22; M-1 to V-21; M-1 to Q-20; M-1 to W-19; M-1 to Q-18; M-1 to G-17; M-1 to S-16; M-1 to G-15; M-1 to L-14; M-1 to K-13; M-1 to L-12; M-1 to L-11; M-1 to S-10; M-1 to L-9; M-1 to V-8 and/or M-1 to L-7 of SEQ ID NO: 20. Polynucleotides encoding these polypeptides are also encompassed by the invention, as are antibodies that bind one or more of these polypeptides. Moreover, fragments and variants of these polypeptides (e.g., fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof) are encompassed by the invention. Antibodies that bind these fragments and variants of the invention are also encompassed by the invention. Polynucleotides encoding these fragments and variants are also encompassed by the invention.

[223] Also as mentioned above, even if deletion of one or more amino acids from the C-terminus of a protein results in modification of loss of one or more biological functions of the protein (e.g., ability to inhibit the Mixed Lymphocyte Reaction), other functional activities

(e.g., biological activities, ability to multimerize, ability to bind receptor, ability to generate antibodies, ability to bind antibodies) may still be retained. For example, the ability of the shortened polypeptide to induce and/or bind to antibodies which recognize the complete or mature forms of the polypeptide generally will be retained when less than the majority of the residues of the complete or mature polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a polypeptide with a large number of deleted C-terminal amino acid residues may retain some biological or immunogenic activities. In fact, peptides composed of as few as six amino acid residues may often evoke an immune response.

[224] More in particular, the invention provides polynucleotides encoding polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group of N-terminal deletions of the mature extracellular portion of the B7-H13 protein (SEQ ID NO: 49): W-19 to V-239; Q-20 to V-239; V-21 to V-239; F-22 to V-239; G-23 to V-239; P-24 to V-239; D-25 to V-239; K-26 to V-239; P-27 to V-239; V-28 to V-239; Q-29 to V-239; A-30 to V-239; L-31 to V-239; V-32 to V-239; G-33 to V-239; E-34 to V-239; D-35 to V-239; A-36 to V-239; A-37 to V-239; F-38 to V-239; S-39 to V-239; C-40 to V-239; F-41 to V-239; L-42 to V-239; S-43 to V-239; P-44 to V-239; K-45 to V-239; T-46 to V-239; N-47 to V-239; A-48 to V-239; E-49 to V-239; A-50 to V-239; M-51 to V-239; E-52 to V-239; V-53 to V-239; R-54 to V-239; F-55 to V-239; F-56 to V-239; R-57 to V-239; G-58 to V-239; Q-59 to V-239; F-60 to V-239; S-61 to V-239; S-62 to V-239; V-63 to V-239; V-64 to V-239; H-65 to V-239; L-66 to V-239; Y-67 to V-239; R-68 to V-239; D-69 to V-239; G-70 to V-239; K-71 to V-239; D-72 to V-239; Q-73 to V-239; P-74 to V-239; F-75 to V-239; M-76 to V-239; Q-77 to V-239; M-78 to V-239; P-79 to V-239; Q-80 to V-239; Y-81 to V-239; Q-82 to V-239; G-83 to V-239; R-84 to V-239; T-85 to V-239; K-86 to V-239; L-87 to V-239; V-88 to V-239; K-89 to V-239; D-90 to V-239; S-91 to V-239; I-92 to V-239; A-93 to V-239; E-94 to V-239; G-95 to V-239; R-96 to V-239; I-97 to V-239; S-98 to V-239; L-99 to V-239; R-100 to V-239; L-101 to V-239; E-102 to V-239; N-103 to V-239; I-104 to V-239; T-105 to V-239; V-106 to V-239; L-107 to V-239; D-108 to V-239; A-109 to V-239; G-110 to V-239; L-111 to V-239; Y-112 to V-239; G-113 to V-239; C-114 to V-239; R-115 to V-239; I-116 to V-239; S-117 to V-239; S-118 to V-239; Q-119 to V-239; S-120 to V-239; Y-121 to V-239;

Y-122 to V-239; Q-123 to V-239; K-124 to V-239; A-125 to V-239; I-126 to V-239; W-127 to V-239; E-128 to V-239; L-129 to V-239; Q-130 to V-239; V-131 to V-239; S-132 to V-239; A-133 to V-239; L-134 to V-239; G-135 to V-239; S-136 to V-239; V-137 to V-239; P-138 to V-239; L-139 to V-239; I-140 to V-239; S-141 to V-239; I-142 to V-239; T-143 to V-239; G-144 to V-239; Y-145 to V-239; V-146 to V-239; D-147 to V-239; R-148 to V-239; D-149 to V-239; I-150 to V-239; Q-151 to V-239; L-152 to V-239; L-153 to V-239; C-154 to V-239; Q-155 to V-239; S-156 to V-239; S-157 to V-239; G-158 to V-239; W-159 to V-239; F-160 to V-239; P-161 to V-239; R-162 to V-239; P-163 to V-239; T-164 to V-239; A-165 to V-239; K-166 to V-239; W-167 to V-239; K-168 to V-239; G-169 to V-239; P-170 to V-239; Q-171 to V-239; G-172 to V-239; Q-173 to V-239; D-174 to V-239; L-175 to V-239; S-176 to V-239; T-177 to V-239; D-178 to V-239; S-179 to V-239; R-180 to V-239; T-181 to V-239; N-182 to V-239; R-183 to V-239; D-184 to V-239; M-185 to V-239; H-186 to V-239; G-187 to V-239; L-188 to V-239; F-189 to V-239; D-190 to V-239; V-191 to V-239; E-192 to V-239; I-193 to V-239; S-194 to V-239; L-195 to V-239; T-196 to V-239; V-197 to V-239; Q-198 to V-239; E-199 to V-239; N-200 to V-239; A-201 to V-239; G-202 to V-239; S-203 to V-239; I-204 to V-239; S-205 to V-239; C-206 to V-239; S-207 to V-239; M-208 to V-239; R-209 to V-239; H-210 to V-239; A-211 to V-239; H-212 to V-239; L-213 to V-239; S-214 to V-239; R-215 to V-239; E-216 to V-239; V-217 to V-239; E-218 to V-239; S-219 to V-239; R-220 to V-239; V-221 to V-239; Q-222 to V-239; I-223 to V-239; G-224 to V-239; D-225 to V-239; T-226 to V-239; F-227 to V-239; F-228 to V-239; E-229 to V-239; P-230 to V-239; I-231 to V-239; S-232 to V-239; W-233 to V-239; and/or H-234 to V-239 of SEQ ID NO: 20. Polynucleotides encoding these polypeptides are also encompassed by the invention, as are antibodies that bind one or more of these polypeptides. Moreover, fragments and variants of these polypeptides (e.g., fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof) are encompassed by the invention. Antibodies that bind these fragments and variants of the invention are also encompassed by the invention. Polynucleotides encoding these fragments and variants are also encompassed by the invention.

[225] Additionally, the invention provides polynucleotides encoding polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group of

C-terminal deletions of the mature extracellular portion of the B7-H13 protein (SEQ ID NO: 49): Q-18 to K-238; Q-18 to T-237; Q-18 to A-236; Q-18 to L-235; Q-18 to H-234; Q-18 to W-233; Q-18 to S-232; Q-18 to I-231; Q-18 to P-230; Q-18 to E-229; Q-18 to F-228; Q-18 to F-227; Q-18 to T-226; Q-18 to D-225; Q-18 to G-224; Q-18 to I-223; Q-18 to Q-222; Q-18 to V-221; Q-18 to R-220; Q-18 to S-219; Q-18 to E-218; Q-18 to V-217; Q-18 to E-216; Q-18 to R-215; Q-18 to S-214; Q-18 to L-213; Q-18 to H-212; Q-18 to A-211; Q-18 to H-210; Q-18 to R-209; Q-18 to M-208; Q-18 to S-207; Q-18 to C-206; Q-18 to S-205; Q-18 to I-204; Q-18 to S-203; Q-18 to G-202; Q-18 to A-201; Q-18 to N-200; Q-18 to E-199; Q-18 to Q-198; Q-18 to V-197; Q-18 to T-196; Q-18 to L-195; Q-18 to S-194; Q-18 to I-193; Q-18 to E-192; Q-18 to V-191; Q-18 to D-190; Q-18 to F-189; Q-18 to L-188; Q-18 to G-187; Q-18 to H-186; Q-18 to M-185; Q-18 to D-184; Q-18 to R-183; Q-18 to N-182; Q-18 to T-181; Q-18 to R-180; Q-18 to S-179; Q-18 to D-178; Q-18 to T-177; Q-18 to S-176; Q-18 to L-175; Q-18 to D-174; Q-18 to Q-173; Q-18 to G-172; Q-18 to Q-171; Q-18 to P-170; Q-18 to G-169; Q-18 to K-168; Q-18 to W-167; Q-18 to K-166; Q-18 to A-165; Q-18 to T-164; Q-18 to P-163; Q-18 to R-162; Q-18 to P-161; Q-18 to F-160; Q-18 to W-159; Q-18 to G-158; Q-18 to S-157; Q-18 to S-156; Q-18 to Q-155; Q-18 to C-154; Q-18 to L-153; Q-18 to L-152; Q-18 to Q-151; Q-18 to I-150; Q-18 to D-149; Q-18 to R-148; Q-18 to D-147; Q-18 to V-146; Q-18 to Y-145; Q-18 to G-144; Q-18 to T-143; Q-18 to I-142; Q-18 to S-141; Q-18 to I-140; Q-18 to L-139; Q-18 to P-138; Q-18 to V-137; Q-18 to S-136; Q-18 to G-135; Q-18 to L-134; Q-18 to A-133; Q-18 to S-132; Q-18 to V-131; Q-18 to Q-130; Q-18 to L-129; Q-18 to E-128; Q-18 to W-127; Q-18 to I-126; Q-18 to A-125; Q-18 to K-124; Q-18 to Q-123; Q-18 to Y-122; Q-18 to Y-121; Q-18 to S-120; Q-18 to Q-119; Q-18 to S-118; Q-18 to S-117; Q-18 to I-116; Q-18 to R-115; Q-18 to C-114; Q-18 to G-113; Q-18 to Y-112; Q-18 to L-111; Q-18 to G-110; Q-18 to A-109; Q-18 to D-108; Q-18 to L-107; Q-18 to V-106; Q-18 to T-105; Q-18 to I-104; Q-18 to N-103; Q-18 to E-102; Q-18 to L-101; Q-18 to R-100; Q-18 to L-99; Q-18 to S-98; Q-18 to I-97; Q-18 to R-96; Q-18 to G-95; Q-18 to E-94; Q-18 to A-93; Q-18 to I-92; Q-18 to S-91; Q-18 to D-90; Q-18 to K-89; Q-18 to V-88; Q-18 to L-87; Q-18 to K-86; Q-18 to T-85; Q-18 to R-84; Q-18 to G-83; Q-18 to Q-82; Q-18 to Y-81; Q-18 to Q-80; Q-18 to P-79; Q-18 to M-78; Q-18 to Q-77; Q-18 to M-76; Q-18 to F-75; Q-18 to P-74; Q-18 to Q-73; Q-18 to D-72; Q-18 to K-71; Q-18 to G-70; Q-18 to D-69; Q-18 to R-68; Q-18 to Y-67; Q-18 to L-66; Q-18 to H-65; Q-18 to V-64; Q-18 to V-63; Q-18 to S-62; Q-18 to S-61; Q-18 to F-60; Q-18 to Q-59; Q-18 to G-58; Q-18 to R-57; Q-18 to F-56; Q-18 to F-55; Q-18

to R-54; Q-18 to V-53; Q-18 to E-52; Q-18 to M-51; Q-18 to A-50; Q-18 to E-49; Q-18 to A-48; Q-18 to N-47; Q-18 to T-46; Q-18 to K-45; Q-18 to P-44; Q-18 to S-43; Q-18 to L-42; Q-18 to F-41; Q-18 to C-40; Q-18 to S-39; Q-18 to F-38; Q-18 to A-37; Q-18 to A-36; Q-18 to D-35; Q-18 to E-34; Q-18 to G-33; Q-18 to V-32; Q-18 to L-31; Q-18 to A-30; Q-18 to Q-29; Q-18 to V-28; Q-18 to P-27; Q-18 to K-26; Q-18 to D-25; and/or Q-18 to P-24 of SEQ ID NO: 20. Polynucleotides encoding these polypeptides are also encompassed by the invention, as are antibodies that bind one or more of these polypeptides. Moreover, fragments and variants of these polypeptides (e.g., fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% identical to these polypeptides and polypeptides encoded by the polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides, or the complement thereof) are encompassed by the invention. Antibodies that bind these fragments and variants of the invention are also encompassed by the invention. Polynucleotides encoding these fragments and variants are also encompassed by the invention.

[226] In addition, any of the above listed N- or C-terminal deletions can be combined to produce a N- and C-terminal deleted polypeptide. The invention also provides polypeptides comprising, or alternatively consisting of, one or more amino acids deleted from both the amino and the carboxyl termini, which may be described generally as having residues m-n of SEQ ID NO: 20, where n and m are integers as described above. Fragments and/or variants of these polypeptides, such as, for example, fragments and/or variants as described herein, are encompassed by the invention. Polynucleotides encoding these polypeptides (including fragments and/or variants) are also encompassed by the invention, as are antibodies that bind these polypeptides.

[227] The present invention is also directed to proteins containing polypeptides at least 80%, 85%, 90%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to a polypeptide sequence set forth herein as m-n. In preferred embodiments, the application is directed to proteins containing polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to polypeptides having the amino acid sequence of the specific N- and C-terminal deletions recited herein. Fragments and/or variants of these polypeptides, such as, for example, fragments and/or variants as described herein, are encompassed by the invention. Polynucleotides encoding these polypeptides (including fragments and/or variants) are also encompassed by the invention, as are antibodies that bind these polypeptides.

[228] Also included are polynucleotide sequences encoding a polypeptide consisting of a portion of the complete amino acid sequence encoded by a cDNA clone contained in ATCC Deposit No. PTA-2332, where this portion excludes any integer of amino acid residues from 1 to about 455 amino acids from the amino terminus of the complete amino acid sequence encoded by a cDNA clone contained in ATCC Deposit No. PTA-2332, or any integer of amino acid residues from 1 to about 455 amino acids from the carboxy terminus, or any combination of the above amino terminal and carboxy terminal deletions, of the complete amino acid sequence encoded by the cDNA clone contained in ATCC Deposit No. PTA-2332. Polypeptides encoded by these polynucleotides also are encompassed by the invention.

[229] As described herein or otherwise known in the art, the polynucleotides of the invention have uses that include, but are not limited to, serving as probes or primers in chromosome identification, chromosome mapping, and linkage analysis.

[230] It has been discovered that this gene is expressed in small intestine and colon tissues.

[231] Polynucleotides, translation products and antibodies corresponding to this gene are useful as reagents for differential identification of gastrointestinal system tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases and/or disorders involving immune system activation, stimulation and/or surveillance, particularly involving T cells, in addition to other immune system cells such as dendritic cells, neutrophils, and leukocytes, as well as diseases and/or disorders of the gastrointestinal system. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). Particularly contemplated are the use of antibodies directed against the extracellular portion of this protein which act as antagonists for the activity of the B7-H13 protein. Such antagonistic antibodies would be useful for the prevention and/or inhibition of such biological activites as are disclosed herein (e.g. T cell modulated activities).

[232] For a number of disorders of the above tissues or cells, particularly of the gastrointestinal and immune systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., gastrointestinal, neural, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a

disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

[233] The homology to members of the B7 family of ligands indicates that the polynucleotides, translation products and antibodies corresponding to this gene are useful for the diagnosis, detection and/or treatment of diseases and/or disorders involving immune system activation, stimulation and/or surveillance, particularly as relating to T cells, neutrophils, dendritic cells, leukocytes, and other immune system cells. In particular, the translation product of the B7-H13 gene may be involved in the costimulation of T cells, binding to ICOS, and/or may play a role in modulation of the expression of particular cytokines, for example.

[234] More generally, the tissue distribution in immune system cells indicates that this gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of immune system origin, polynucleotides, translation products and antibodies corresponding to this gene may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

[235] Polynucleotides, translation products and antibodies corresponding to this gene may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Additionally, polynucleotides, translation products and antibodies corresponding to this gene may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement.

[236] Expression within gastrointestinal tissue indicates that polynucleotides, translation products and antibodies corresponding to this gene are useful for the diagnosis and/or treatment of disorders involving the small intestine. This may include diseases associated with digestion and food absorption, as well as hematopoietic disorders involving the Peyer's patches of the small intestine, or other hematopoietic cells and tissues within the body.

Similarly, expression of this gene product in colon tissue suggests again involvement in digestion, processing, and elimination of food, as well as a potential role for this gene as a diagnostic marker or causative agent in the development of colon cancer, and cancer in general. Additionally, translation products corresponding to this gene, as well as antibodies directed against these translation products, may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

TABLE 1

Gene No.	cDNA Plasmid:V	ATCC Deposit No:Z and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	AA SEQ ID NO: Y	Last AA of ORF
1	HE8NC81	PTA-2332 08/07/00	Uni-ZAP XR	2	3357	1	3357	419	14	282
1	HE8NC81	PTA-2332 08/07/00	Uni-ZAP XR	9	2626	1	2626	74	21	13
2	HDPPA04	PTA-2332 08/07/00	pCMVSpor t 3.0	3	2406	1	2406	271	15	283
2	HDPPA04	PTA-2332 08/07/00	pCMVSpor t 3.0	10	1675	1	1613		22	23
2	HDPPA04	PTA-2332 08/07/00	pCMVSpor t 3.0	11	786	1	786	261	23	93
3	HTTDB46	PTA-2332 08/07/00	Uni-ZAP XR	4	3059	1	3059	55	16	318
3	HTTDB46	PTA-2332 08/07/00	Uni-ZAP XR	12	2008	215	2008	153	24	461
4	HCECR39	PTA-2332 08/07/00	Uni-ZAP XR	5	2682	1	2682	135	17	454
4	HCECR39	PTA-2332 08/07/00	Uni-ZAP XR	13	2799	122	2799	249	25	402
5	HCE2X64	PTA-2332 08/07/00	Uni-ZAP XR	6	1726	1	1726	219	18	414
6	HEMFH17	PTA-2332 08/07/00	Uni-ZAP XR	7	1021	1	1021	135	19	159
7	HSIDS22	PTA-2332 08/07/00	Uni-ZAP XR	8	1835	1	1835	9	20	461

[237] Table 1 summarizes the information corresponding to each "Gene No:" described above. The nucleotide sequence identified as "NT SEQ ID NO:X" was assembled from partially homologous ("overlapping") sequences obtained from the "cDNA Plasmid:V" identified in Table 1 and, in some cases, from additional related DNA clones. The overlapping sequences were assembled into a single contiguous sequence of high redundancy (usually three to five overlapping sequences at each nucleotide position), resulting in a final sequence identified as SEQ ID NO:X.

[238] The cDNA Plasmid:V was deposited on the date and given the corresponding deposit number listed in "ATCC Deposit No:Z and Date." Some of the deposits contain multiple different clones corresponding to the same gene. "Vector" refers to the type of vector contained in cDNA Plasmid:V.

[239] "Total NT Seq." refers to the total number of nucleotides in the contig identified by "Gene No:". The deposited plasmid contains all of these sequences, reflected by the nucleotide position indicated as "5' NT of Clone Seq." and the "3' NT of Clone Seq." of SEQ ID NO:X. The nucleotide position of SEQ ID NO:X of the putative methionine start codon (if present) is identified as "5' NT of Start Codon." Similarly, the nucleotide position of SEQ ID NO:X of the predicted signal sequence (if present) is identified as "5' NT of First AA of Signal Pep."

[240] The translated amino acid sequence, beginning with the first translated codon of the polynucleotide sequence, is identified as "AA SEQ ID NO:Y," although other reading frames can also be easily translated using known molecular biology techniques. The polypeptides produced by these alternative open reading frames are specifically contemplated by the present invention.

[241] SEQ ID NO:X (where X may be any of the polynucleotide sequences disclosed in the sequence listing) and the translated SEQ ID NO:Y (where Y may be any of the polypeptide sequences disclosed in the sequence listing) are sufficiently accurate and otherwise suitable for a variety of uses well known in the art and described further below. For instance, SEQ ID NO:X has uses including, but not limited to, in designing nucleic acid hybridization probes that will detect nucleic acid sequences contained in SEQ ID NO:X or the cDNA contained in a deposited plasmid. These probes will also hybridize to nucleic acid molecules in biological samples, thereby enabling a variety of forensic and diagnostic

methods of the invention. Similarly, polypeptides identified from SEQ ID NO:Y have uses that include, but are not limited to generating antibodies, which bind specifically to the secreted proteins encoded by the cDNA clones identified in Table 1.

[242] Nevertheless, DNA sequences generated by sequencing reactions can contain sequencing errors. The errors exist as misidentified nucleotides, or as insertions or deletions of nucleotides in the generated DNA sequence. The erroneously inserted or deleted nucleotides cause frame shifts in the reading frames of the predicted amino acid sequence. In these cases, the predicted amino acid sequence diverges from the actual amino acid sequence, even though the generated DNA sequence may be greater than 99.9% identical to the actual DNA sequence (for example, one base insertion or deletion in an open reading frame of over 1000 bases).

[243] Accordingly, for those applications requiring precision in the nucleotide sequence or the amino acid sequence, the present invention provides not only the generated nucleotide sequence identified as SEQ ID NO:X, and the predicted translated amino acid sequence identified as SEQ ID NO:Y, but also a sample of plasmid DNA containing a human cDNA of the invention deposited with the ATCC, as set forth in Table 1. The nucleotide sequence of each deposited plasmid can readily be determined by sequencing the deposited plasmid in accordance with known methods.

[244] The predicted amino acid sequence can then be verified from such deposits. Moreover, the amino acid sequence of the protein encoded by a particular plasmid can also be directly determined by peptide sequencing or by expressing the protein in a suitable host cell containing the deposited human cDNA, collecting the protein, and determining its sequence.

[245] Also provided in Table 1 is the name of the vector which contains the cDNA plasmid. Each vector is routinely used in the art. The following additional information is provided for convenience.

[246] Vectors Lambda Zap (U.S. Patent Nos. 5,128,256 and 5,286,636), Uni-Zap XR (U.S. Patent Nos. 5,128, 256 and 5,286,636), Zap Express (U.S. Patent Nos. 5,128,256 and 5,286,636), pBluescript (pBS) (Short, J. M. et al., *Nucleic Acids Res. 16:*7583-7600 (1988); Alting-Mees, M. A. and Short, J. M., *Nucleic Acids Res. 17:*9494 (1989)) and pBK (Alting-Mees, M. A. et al., *Strategies 5:*58-61 (1992)) are commercially available from Stratagene Cloning Systems, Inc., 11011 N. Torrey Pines Road, La Jolla, CA, 92037. pBS contains an ampicillin resistance gene and pBK contains a neomycin resistance gene. Phagemid pBS

may be excised from the Lambda Zap and Uni-Zap XR vectors, and phagemid pBK may be excised from the Zap Express vector. Both phagemids may be transformed into *E. coli* strain XL-1 Blue, also available from Stratagene.

[247] Vectors pSport1, pCMVSport 1.0, pCMVSport 2.0 and pCMVSport 3.0, were obtained from Life Technologies, Inc., P. O. Box 6009, Gaithersburg, MD 20897. All Sport vectors contain an ampicillin resistance gene and may be transformed into *E. coli* strain DH10B, also available from Life Technologies. See, for instance, Gruber, C. E., et al., *Focus 15:*59 (1993). Vector lafmid BA (Bento Soares, Columbia University, New York, NY) contains an ampicillin resistance gene and can be transformed into *E. coli* strain XL-1 Blue. Vector pCR®2.1, which is available from Invitrogen, 1600 Faraday Avenue, Carlsbad, CA 92008, contains an ampicillin resistance gene and may be transformed into *E. coli* strain DH10B, available from Life Technologies. See, for instance, Clark, J. M., *Nuc. Acids Res. 16:*9677-9686 (1988) and Mead, D. *et al., Bio/Technology 9:* (1991).

[248] The present invention also relates to the genes corresponding to SEQ ID NO:X, SEQ ID NO:Y, and/or a deposited plasmid (cDNA plasmid:V). The corresponding gene can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include, but are not limited to, preparing probes or primers from the disclosed sequence and identifying or amplifying the corresponding gene from appropriate sources of genomic material.

[249] Also provided in the present invention are allelic variants, orthologs, and/or species homologs. Procedures known in the art can be used to obtain full-length genes, allelic variants, splice variants, full-length coding portions, orthologs, and/or species homologs of genes corresponding to SEQ ID NO:X, SEQ ID NO:Y, and/or cDNA plasmid:V, using information from the sequences disclosed herein or the clones deposited with the ATCC. For example, allelic variants and/or species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source for allelic variants and/or the desired homologue.

[250] The present invention provides a polynucleotide comprising, or alternatively consisting of, the nucleic acid sequence of SEQ ID NO:X and/or cDNA plasmid:V. The present invention also provides a polypeptide comprising, or alternatively, consisting of, the polypeptide sequence of SEQ ID NO:Y, a polypeptide encoded by SEQ ID NO:X, and/or a polypeptide encoded by the cDNA in cDNA plasmid:V. Polynucleotides encoding a

polypeptide comprising, or alternatively consisting of the polypeptide sequence of SEQ ID NO:Y, a polypeptide encoded by SEQ ID NO:X and/or a polypeptide encoded by the cDNA in cDNA plasmid:V, are also encompassed by the invention. The present invention further encompasses a polynucleotide comprising, or alternatively consisting of the complement of the nucleic acid sequence of SEQ ID NO:X, and/or the complement of the coding strand of the cDNA in cDNA plasmid:V.

[251] Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would unduly burden the disclosure of this application. Accordingly, preferably excluded from SEQ ID NO:X are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 and the final nucleotide minus 15 of SEQ ID NO:X, b is an integer of 15 to the final nucleotide of SEQ ID NO:X, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:X, and where b is greater than or equal to a + 14.

RACE Protocol For Recovery of Full-Length Genes

[252] Partial cDNA clones can be made full-length by utilizing the rapid amplification of cDNA ends (RACE) procedure described in Frohman, M.A., et al., Proc. Nat'l. Acad. Sci. USA, 85:8998-9002 (1988). A cDNA clone missing either the 5' or 3' end can be reconstructed to include the absent base pairs extending to the translational start or stop codon, respectively. In some cases, cDNAs are missing the start of translation, therefor. The following briefly describes a modification of this original 5' RACE procedure. Poly A+ or total RNA is reverse transcribed with Superscript II (Gibco/BRL) and an antisense or complementary primer specific to the cDNA sequence. The primer is removed from the reaction with a Microcon Concentrator (Amicon). The first-strand cDNA is then tailed with dATP and terminal deoxynucleotide transferase (Gibco/BRL). Thus, an anchor sequence is produced which is needed for PCR amplification. The second strand is synthesized from the dA-tail in PCR buffer, Taq DNA polymerase (Perkin-Elmer Cetus), an oligo-dT primer containing three adjacent restriction sites (XhoI, SalI and ClaI) at the 5' end and a primer containing just these restriction sites. This double-stranded cDNA is PCR amplified for 40

cycles with the same primers as well as a nested cDNA-specific antisense primer. The PCR products are size-separated on an ethidium bromide-agarose gel and the region of gel containing cDNA products the predicted size of missing protein-coding DNA is removed. cDNA is purified from the agarose with the Magic PCR Prep kit (Promega), restriction digested with XhoI or SalI, and ligated to a plasmid such as pBluescript SKII (Stratagene) at XhoI and EcoRV sites. This DNA is transformed into bacteria and the plasmid clones sequenced to identify the correct protein-coding inserts. Correct 5' ends are confirmed by comparing this sequence with the putatively identified homologue and overlap with the partial cDNA clone. Similar methods known in the art and/or commercial kits are used to amplify and recover 3' ends.

[253] Several quality-controlled kits are commercially available for purchase. Similar reagents and methods to those above are supplied in kit form from Gibco/BRL for both 5' and 3' RACE for recovery of full length genes. A second kit is available from Clontech which is a modification of a related technique, SLIC (single-stranded ligation to single-stranded cDNA), developed by Dumas et al., Nucleic Acids Res., 19:5227-32 (1991). The major differences in procedure are that the RNA is alkaline hydrolyzed after reverse transcription and RNA ligase is used to join a restriction site-containing anchor primer to the first-strand cDNA. This obviates the necessity for the dA-tailing reaction which results in a polyT stretch that is difficult to sequence past.

[254] An alternative to generating 5' or 3' cDNA from RNA is to use cDNA library double-stranded DNA. An asymmetric PCR-amplified antisense cDNA strand is synthesized with an antisense cDNA-specific primer and a plasmid-anchored primer. These primers are removed and a symmetric PCR reaction is performed with a nested cDNA-specific antisense primer and the plasmid-anchored primer.

RNA Ligase Protocol For Generating The 5' or 3' End Sequences To Obtain Full Length Genes

[255] Once a gene of interest is identified, several methods are available for the identification of the 5' or 3' portions of the gene which may not be present in the original cDNA plasmid. These methods include, but are not limited to, filter probing, clone enrichment using specific probes and protocols similar and identical to 5' and 3'RACE. While the full length gene may be present in the library and can be identified by probing, a

useful method for generating the 5' or 3' end is to use the existing sequence information from the original cDNA to generate the missing information. A method similar to 5'RACE is available for generating the missing 5' end of a desired full-length gene. (This method was published by Fromont-Racine et al., Nucleic Acids Res., 21(7):1683-1684 (1993)). Briefly, a specific RNA oligonucleotide is ligated to the 5' ends of a population of RNA presumably containing full-length gene RNA transcript and a primer set containing a primer specific to the ligated RNA oligonucleotide and a primer specific to a known sequence of the gene of interest, is used to PCR amplify the 5' portion of the desired full length gene which may then be sequenced and used to generate the full length gene. This method starts with total RNA isolated from the desired source, poly A RNA may be used but is not a prerequisite for this procedure. The RNA preparation may then be treated with phosphatase if necessary to eliminate 5' phosphate groups on degraded or damaged RNA which may interfere with the later RNA ligase step. The phosphatase if used is then inactivated and the RNA is treated with tobacco acid pyrophosphatase in order to remove the cap structure present at the 5' ends of messenger RNAs. This reaction leaves a 5' phosphate group at the 5' end of the cap cleaved RNA which can then be ligated to an RNA oligonucleotide using T4 RNA ligase. This modified RNA preparation can then be used as a template for first strand cDNA synthesis using a gene specific oligonucleotide. The first strand synthesis reaction can then be used as a template for PCR amplification of the desired 5' end using a primer specific to the ligated RNA oligonucleotide and a primer specific to the known sequence of the B7-like gene of interest. The resultant product is then sequenced and analyzed to confirm that the 5' end sequence belongs to the relevant B7-like gene.

Polynucleotide and Polypeptide Fragments

[256] The present invention is also directed to polynucleotide fragments of the polynucleotides (nucleic acids) of the invention. In the present invention, a "polynucleotide fragment" refers to a polynucleotide having a nucleic acid sequence which: is a portion of the cDNA contained in cDNA plasmid:V or encoding the polypeptide encoded by the cDNA contained in cDNA plasmid:V; is a portion of the polynucleotide sequence in SEQ ID NO:X or the complementary strand thereto; is a polynucleotide sequence encoding a portion of the polypeptide of SEQ ID NO:Y; or is a polynucleotide sequence encoding a portion of a polypeptide encoded by SEQ ID NO:X. The nucleotide fragments of the invention are

preferably at least about 15 nt, and more preferably at least about 20 nt, still more preferably at least about 30 nt, and even more preferably, at least about 40 nt, at least about 50 nt, at least about 75 nt, at least about 100 nt, at least about 125 nt, or at least about 150 nt in length. A fragment "at least 20 nt in length," for example, is intended to include 20 or more contiguous bases from, for example, the sequence contained in the cDNA in cDNA plasmid:V, or the nucleotide sequence shown in SEQ ID NO:X or the complementary stand thereto. In this context "about" includes the particularly recited value, or a value larger or smaller by several (5, 4, 3, 2, or 1) nucleotides. These nucleotide fragments have uses that include, but are not limited to, as diagnostic probes and primers as discussed herein. Of course, larger fragments (e.g., at least 150, 175, 200, 250, 500, 600, 1000, or 2000 nucleotides in length) are also encompassed by the invention.

[257] Moreover, representative examples of polynucleotide fragments of the invention, include, for example, fragments comprising, or alternatively consisting of, a sequence from about nucleotide number 1-50, 51-100, 101-150, 151-200, 201-250, 251-300, 301-350, 351-400, 401-450, 451-500, 501-550, 551-600, 651-700,701- 750, 751-800, 800-850, 851-900, 901-950, 951-1000, 1001-1050, 1051-1100, 1101-1150, 1151-1200, 1201-1250, 1251-1300, 1301-1350, 1351-1400, 1401-1450, 1451-1500, 1501-1550, 1551-1600, 1601-1650, 1651-1700, 1701-1750, 1751-1800, 1801-1850, 1851-1900, 1901-1950, 1951-2000, 2001-2050, 2051-2100, 2101-2150, 2151-2200, 2201-2250, 2251-2300, 2301-2350, 2351-2400, 2401-2450, 2451-2500, 2501-2550, 2551-2600, 2601-2650, 2651-2700, 2701-2750, 2751-2800, 2801-2850, 2851-2900, 2901-2950, 2951-3000, 3001-3050, 3051-3100, 3101-3150, 3151-3200, 3201-3250, 3251-3300, and/or 3301-3357 of SEQ ID NO:X, or the complementary strand thereto. In this context "about" includes the particularly recited range or a range larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Preferably, these fragments encode a polypeptide which has a functional activity (e.g. biological activity) of the polypeptide encoded by a polynucleotide of which the sequence is a portion. More preferably, these fragments can be used as probes or primers as discussed herein. Polynucleotides which hybridize to one or more of these fragments under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention, as are polypeptides encoded by these polynucleotides or fragments.

[258] Moreover, representative examples of polynucleotide fragments of the invention, include, for example, fragments comprising, or alternatively consisting of, a sequence from about nucleotide number 1-50, 51-100, 101-150, 151-200, 201-250, 251-300, 301-350, 351-400, 401-450, 451-500, 501-550, 551-600, 601-650, 651-700, 701-750, 751-800, 801-850, 851-900, 901-950, 951-1000, 1001-1050, 1051-1100, 1101-1150, 1151-1200, 1201-1250, 1251-1300, 1301-1350, 1351-1400, 1401-1450, 1451-1500, 1501-1550, 1551-1600, 1601-1650, 1651-1700, 1701-1750, 1751-1800, 1801-1850, 1851-1900, 1901-1950, 1951-2000, 2001-2050, 2051-2100, 2101-2150, 2151-2200, 2201-2250, 2251-2300, 2301-2350, 2351-2400, 2401-2450, 2451-2500, 2501-2550, 2551-2600, 2601-2650, 2651-2700, 2701-2750, 2751-2800, 2801-2850, 2851-2900, 2901-2950, 2951-3000, 3001-3050, 3051-3100, 3101-3150, 3151-3200, 3201-3250, 3251-3300, and/or 3301-3357 of the cDNA nucleotide sequence contained in cDNA plasmid:V, or the complementary strand thereto. In this context "about" includes the particularly recited range or a range larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Preferably, these fragments encode a polypeptide which has a functional activity (e.g. biological activity) of the polypeptide encoded by the cDNA nucleotide sequence contained in cDNA plasmid:V. More preferably, these fragments can be used as probes or primers as discussed herein. Polynucleotides which hybridize to one or more of these fragments under stringent hybridization conditions, or alternatively, under lower stringency conditions are also encompassed by the invention, as are polypeptides encoded by these polynucleotides or fragments.

[259] In the present invention, a "polypeptide fragment" refers to an amino acid sequence which is a portion of that contained in SEQ ID NO:Y, a portion of an amino acid sequence encoded by the polynucleotide sequence of SEQ ID NO:X, and/or encoded by the cDNA in cDNA plasmid:V. Protein (polypeptide) fragments may be "free-standing," or comprised within a larger polypeptide of which the fragment forms a part or region, most preferably as a single continuous region. Representative examples of polypeptide fragments of the invention, include, for example, fragments comprising, or alternatively consisting of, an amino acid sequence from about amino acid number 1-20, 21-40, 41-60, 61-80, 81-100, 101-120, 121-140, 141-160, 161-180, 181-200, 201-220, 221-240, 241-260, 261-280, 281-300, 301-320, 321-340, 341-360, 361-380, 381-400, 401-420, 421-440, and/or 441-461 of the coding region of SEQ ID NO:Y. Moreover, polypeptide fragments of the invention may be at least about 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 100, 110, 120,

130, 140, or 150 amino acids in length. In this context "about" includes the particularly recited ranges or values, or ranges or values larger or smaller by several (5, 4, 3, 2, or 1) amino acids, at either terminus or at both termini. Polynucleotides encoding these polypeptide fragments are also encompassed by the invention.

[260] Even if deletion of one or more amino acids from the N-terminus of a protein results in modification of loss of one or more biological functions of the protein, other functional activities (e.g., biological activities, ability to multimerize, ability to bind a ligand) may still be retained. For example, the ability of shortened muteins to induce and/or bind to antibodies which recognize the complete or mature forms of the polypeptides generally will be retained when less than the majority of the residues of the complete or mature polypeptide are removed from the N-terminus. Whether a particular polypeptide lacking N-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a mutein with a large number of deleted N-terminal amino acid residues may retain some biological or immunogenic activities. In fact, peptides composed of as few as six amino acid residues may often evoke an immune response.

[261] Accordingly, polypeptide fragments of the invention include the secreted protein as well as the mature form. Further preferred polypeptide fragments include the secreted protein or the mature form having a continuous series of deleted residues from the amino or the carboxy terminus, or both. For example, any number of amino acids, ranging from 1-60, can be deleted from the amino terminus of either the secreted polypeptide or the mature form. Similarly, any number of amino acids, ranging from 1-30, can be deleted from the carboxy terminus of the secreted protein or mature form. Furthermore, any combination of the above amino and carboxy terminus deletions are preferred. Similarly, polynucleotides encoding these polypeptide fragments are also preferred.

[262] The present invention further provides polypeptides having one or more residues deleted from the amino terminus of the amino acid sequence of a polypeptide disclosed herein (e.g., a polypeptide of SEQ ID NO:Y, a polypeptide encoded by the polynucleotide sequence contained in SEQ ID NO:X, and/or a polypeptide encoded by the cDNA contained in cDNA plasmid:V). In particular, N-terminal deletions may be described by the general formula m-q, where q is a whole integer representing the total number of amino acid residues in a polypeptide of the invention (e.g., the polypeptide disclosed in SEQ ID NO:Y), and m is

defined as any integer ranging from 2 to q-6. Polynucleotides encoding these polypeptides, including fragments and/or variants, are also encompassed by the invention.

[263] Also as mentioned above, even if deletion of one or more amino acids from the C-terminus of a protein results in modification of loss of one or more biological functions of the protein, other functional activities (e.g., biological activities, ability to multimerize, ability to bind a ligand) may still be retained. For example the ability of the shortened mutein to induce and/or bind to antibodies which recognize the complete or mature forms of the polypeptide generally will be retained when less than the majority of the residues of the complete or mature polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a mutein with a large number of deleted C-terminal amino acid residues may retain some biological or immunogenic activities. In fact, peptides composed of as few as six amino acid residues may often evoke an immune response.

[264] Accordingly, the present invention further provides polypeptides having one or more residues from the carboxy terminus of the amino acid sequence of a polypeptide disclosed herein (e.g., a polypeptide of SEQ ID NO:Y, a polypeptide encoded by the polynucleotide sequence contained in SEQ ID NO:X, and/or a polypeptide encoded by the cDNA contained in cDNA plasmid:V). In particular, C-terminal deletions may be described by the general formula 1-n, where n is any whole integer ranging from 6 to q-1, and where n corresponds to the position of an amino acid residue in a polypeptide of the invention. Polynucleotides encoding these polypeptides, including fragments and/or variants, are also encompassed by the invention.

[265] In addition, any of the above described N- or C-terminal deletions can be combined to produce a N- and C-terminal deleted polypeptide. The invention also provides polypeptides having one or more amino acids deleted from both the amino and the carboxyl termini, which may be described generally as having residues m-n of a polypeptide encoded by SEQ ID NO:X (e.g., including, but not limited to, the preferred polypeptide disclosed as SEQ ID NO:Y), and/or the cDNA in cDNA plasmid:V, and/or the complement thereof, where n and m are integers as described above. Polynucleotides encoding these polypeptides, including fragments and/or variants, are also encompassed by the invention.

[266] Any polypeptide sequence contained in the polypeptide of SEQ ID NO:Y, encoded

by the polynucleotide sequences set forth as SEQ ID NO:X, or encoded by the cDNA in cDNA plasmid:V may be analyzed to determine certain preferred regions of the polypeptide. For example, the amino acid sequence of a polypeptide encoded by a polynucleotide sequence of SEQ ID NO:X or the cDNA in cDNA plasmid:V may be analyzed using the default parameters of the DNASTAR computer algorithm (DNASTAR, Inc., 1228 S. Park St., Madison, WI 53715 USA; http://www.dnastar.com/).

[267] Polypeptide regions that may be routinely obtained using the DNASTAR computer algorithm include, but are not limited to, Garnier-Robson alpha-regions, beta-regions, turn-regions, and coil-regions, Chou-Fasman alpha-regions, beta-regions, and turn-regions, Kyte-Doolittle hydrophilic regions and hydrophobic regions, Eisenberg alpha- and beta-amphipathic regions, Karplus-Schulz flexible regions, Emini surface-forming regions and Jameson-Wolf regions of high antigenic index. Among highly preferred polynucleotides of the invention in this regard are those that encode polypeptides comprising regions that combine several structural features, such as several (e.g., 1, 2, 3 or 4) of the features set out above.

[268] Additionally, Kyte-Doolittle hydrophilic regions and hydrophobic regions, Emini surface-forming regions, and Jameson-Wolf regions of high antigenic index (i.e., containing four or more contiguous amino acids having an antigenic index of greater than or equal to 1.5, as identified using the default parameters of the Jameson-Wolf program) can routinely be used to determine polypeptide regions that exhibit a high degree of potential for antigenicity. Regions of high antigenicity are determined from data by DNASTAR analysis by choosing values which represent regions of the polypeptide which are likely to be exposed on the surface of the polypeptide in an environment in which antigen recognition may occur in the process of initiation of an immune response.

[269] Preferred polypeptide fragments of the invention are fragments comprising, or alternatively, consisting of, an amino acid sequence that displays a functional activity (e.g. biological activity) of the polypeptide sequence of which the amino acid sequence is a fragment. By a polypeptide displaying a "functional activity" is meant a polypeptide capable of one or more known functional activities associated with a full-length protein, such as, for example, biological activity, antigenicity, immunogenicity, and/or multimerization, as described supra.

[270] Other preferred polypeptide fragments are biologically active fragments. Biologically active fragments are those exhibiting activity similar, but not necessarily identical, to an activity of the polypeptide of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.

[271] In preferred embodiments, polypeptides of the invention comprise, or alternatively consist of, one, two, three, four, five or more of the antigenic fragments of the polypeptide of SEQ ID NO:Y, or portions thereof. Polynucleotides encoding these polypeptides, including fragments and/or variants, are also encompassed by the invention.

[272] The present invention encompasses polypeptides comprising, or alternatively consisting of, an epitope of the polypeptide sequence shown in SEQ ID NO:Y, or an epitope of the polypeptide sequence encoded by the cDNA in cDNA plasmid:V, or encoded by a polynucleotide that hybridizes to the complement of an epitope encoding sequence of SEQ ID NO:X, or an epitope encoding sequence contained in cDNA plasmid:V under stringent hybridization conditions, or alternatively, under lower stringency hybridization, as defined supra. The present invention further encompasses polynucleotide sequences encoding an epitope of a polypeptide sequence of the invention (such as, for example, the sequence disclosed in SEQ ID NO:X), polynucleotide sequences of the complementary strand of a polynucleotide sequence encoding an epitope of the invention, and polynucleotide sequences which hybridize to this complementary strand under stringent hybridization conditions, or alternatively, under lower stringency hybridization conditions, as defined supra.

[273] The term "epitopes," as used herein, refers to portions of a polypeptide having antigenic or immunogenic activity in an animal, preferably a mammal, and most preferably in a human. In a preferred embodiment, the present invention encompasses a polypeptide comprising an epitope, as well as the polynucleotide encoding this polypeptide. An "immunogenic epitope," as used herein, is defined as a portion of a protein that elicits an antibody response in an animal, as determined by any method known in the art, for example, by the methods for generating antibodies described infra. (See, for example, Geysen et al., Proc. Natl. Acad. Sci. USA 81:3998- 4002 (1983)). The term "antigenic epitope," as used herein, is defined as a portion of a protein to which an antibody can immunospecifically bind its antigen as determined by any method well known in the art, for example, by the immunoassays described herein. Immunospecific binding excludes non-specific binding but

does not necessarily exclude cross- reactivity with other antigens. Antigenic epitopes need not necessarily be immunogenic.

[274] Fragments which function as epitopes may be produced by any conventional means. (See, e.g., Houghten, R. A., Proc. Natl. Acad. Sci. USA 82:5131-5135 (1985) further described in U.S. Patent No. 4,631,211.)

[275] In the present invention, antigenic epitopes preferably contain a sequence of at least 4, at least 5, at least 6, at least 7, more preferably at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 20, at least 25, at least 30, at least 40, at least 50, and, most preferably, between about 15 to about 30 amino acids. Preferred polypeptides comprising immunogenic or antigenic epitopes are at least 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 amino acid residues in length. Additional non-exclusive preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as portions thereof. Antigenic epitopes are useful, for example, to raise antibodies, including monoclonal antibodies, that specifically bind the epitope. Preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as any combination of two, three, four, five or more of these antigenic epitopes. Antigenic epitopes can be used as the target molecules in immunoassays. (See, for instance, Wilson et al., Cell 37:767-778 (1984); Sutcliffe et al., Science 219:660-666 (1983)).

[276] Similarly, immunogenic epitopes can be used, for example, to induce antibodies according to methods well known in the art. (See, for instance, Sutcliffe et al., supra; Wilson et al., supra; Chow et al., Proc. Natl. Acad. Sci. USA 82:910-914; and Bittle et al., J. Gen. Virol. 66:2347-2354 (1985). Preferred immunogenic epitopes include the immunogenic epitopes disclosed herein, as well as any combination of two, three, four, five or more of these immunogenic epitopes. The polypeptides comprising one or more immunogenic epitopes may be presented for eliciting an antibody response together with a carrier protein, such as an albumin, to an animal system (such as rabbit or mouse), or, if the polypeptide is of sufficient length (at least about 25 amino acids), the polypeptide may be presented without a carrier. However, immunogenic epitopes comprising as few as 8 to 10 amino acids have been shown to be sufficient to raise antibodies capable of binding to, at the very least, linear epitopes in a denatured polypeptide (e.g., in Western blotting).

[277] Epitope-bearing polypeptides of the present invention may be used to induce antibodies according to methods well known in the art including, but not limited to, in vivo

immunization, in vitro immunization, and phage display methods. See, e.g., Sutcliffe et al., supra; Wilson et al., supra, and Bittle et al., J. Gen. Virol., 66:2347-2354 (1985). If in vivo immunization is used, animals may be immunized with free peptide; however, anti-peptide antibody titer may be boosted by coupling the peptide to a macromolecular carrier, such as keyhole limpet hemacyanin (KLH) or tetanus toxoid. For instance, peptides containing cysteine residues may be coupled to a carrier using a linker such as maleimidobenzoyl- N-hydroxysuccinimide ester (MBS), while other peptides may be coupled to carriers using a more general linking agent such as glutaraldehyde. Animals such as rabbits, rats and mice are immunized with either free or carrier- coupled peptides, for instance, by intraperitoneal and/or intradermal injection of emulsions containing about 100 μg of peptide or carrier protein and Freund's adjuvant or any other adjuvant known for stimulating an immune response. Several booster injections may be needed, for instance, at intervals of about two weeks, to provide a useful titer of anti-peptide antibody which can be detected, for example, by ELISA assay using free peptide adsorbed to a solid surface. The titer of anti-peptide antibodies in serum from an immunized animal may be increased by selection of anti-peptide antibodies, for instance, by adsorption to the peptide on a solid support and elution of the selected antibodies according to methods well known in the art.

[278] As one of skill in the art will appreciate, and as discussed above, the polypeptides of the present invention and immunogenic and/or antigenic epitope fragments thereof can be fused to other polypeptide sequences. For example, the polypeptides of the present invention may be fused with the constant domain of immunoglobulins (IgA, IgE, IgG, IgM), or portions thereof (CH1, CH2, CH3, or any combination thereof and portions thereof) resulting in chimeric polypeptides. Such fusion proteins may facilitate purification and may increase half-life in vivo. This has been shown for chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. See, e.g., EP 394,827; Traunecker et al., Nature, 331:84-86 (1988). Enhanced delivery of an antigen across the epithelial barrier to the immune system has been demonstrated for antigens (e.g., insulin) conjugated to an FcRn binding partner such as IgG or Fc fragments (see, e.g., PCT Publications WO 96/22024 and WO 99/04813). IgG Fusion proteins that have a disulfide-linked dimeric structure due to the IgG portion desulfide bonds have also been found to be more efficient in binding and

neutralizing other molecules than monomeric polypeptides or fragments thereof alone. See, e.g., Fountoulakis et al., J. Biochem., 270:3958-3964 (1995).

[279] Similarly, EP-A-O 464 533 (Canadian counterpart 2045869) discloses fusion proteins comprising various portions of constant region of immunoglobulin molecules together with another human protein or part thereof. In many cases, the Fc part in a fusion protein is beneficial in therapy and diagnosis, and thus can result in, for example, improved pharmacokinetic properties. (EP-A 0232 262.) Alternatively, deleting the Fc part after the fusion protein has been expressed, detected, and purified, may be desired. For example, the Fc portion may hinder therapy and diagnosis if the fusion protein is used as an antigen for immunizations. In drug discovery, for example, human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. (See, D. Bennett et al., J. Molecular Recognition 8:52-58 (1995); K. Johanson et al., J. Biol. Chem. 270:9459-9471 (1995)).

[280] Moreover, the polypeptides of the present invention can be fused to marker sequences, such as a peptide which facilitates purification of the fused polypeptide. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et al., Proc. Natl. Acad. Sci. USA 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Another peptide tag useful for purification, the "HA" tag, corresponds to an epitope derived from the influenza hemagglutinin protein. (Wilson et al., Cell 37:767 (1984)).

[281] Thus, any of these above fusions can be engineered using the polynucleotides or the polypeptides of the present invention.

[282] Nucleic acids encoding the above epitopes can also be recombined with a gene of interest as an epitope tag (e.g., the hemagglutinin ("HA") tag or flag tag) to aid in detection and purification of the expressed polypeptide. For example, a system described by Janknecht et al. allows for the ready purification of non-denatured fusion proteins expressed in human cell lines (Janknecht et al., Proc. Natl. Acad. Sci. USA 88:8972- 897 (1991)). In this system, the gene of interest is subcloned into a vaccinia recombination plasmid such that the open reading frame of the gene is translationally fused to an amino-terminal tag consisting of six histidine residues. The tag serves as a matrix binding domain for the fusion

protein. Extracts from cells infected with the recombinant vaccinia virus are loaded onto Ni2+ nitriloacetic acid-agarose column and histidine-tagged proteins can be selectively eluted with imidazole-containing buffers.

[283] Additional fusion proteins of the invention may be generated through the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling"). DNA shuffling may be employed to modulate the activities of polypeptides of the invention, such methods can be used to generate polypeptides with altered activity, as well as agonists and antagonists of the polypeptides. See, generally, U.S. Patent Nos. 5,605,793; 5,811,238; 5,830,721; 5,834,252; and 5,837,458, and Patten et al., Curr. Opinion Biotechnol. 8:724-33 (1997); Harayama, Trends Biotechnol. 16(2):76-82 (1998); Hansson, et al., J. Mol. Biol. 287:265-76 (1999); and Lorenzo and Blasco, Biotechniques 24(2):308- 13 (1998) (each of these patents and publications are hereby incorporated by reference in its entirety). In one embodiment, alteration of polynucleotides corresponding to SEQ ID NO:X and the polypeptides encoded by these polynucleotides may be achieved by DNA shuffling. DNA shuffling involves the assembly of two or more DNA segments by homologous or site-specific recombination to generate variation in the polynucleotide sequence. In another embodiment, polynucleotides of the invention, or the encoded polypeptides, may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. In another embodiment, one or more components, motifs, sections, parts, domains, fragments, etc., of a polynucleotide encoding a polypeptide of the invention may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules.

Polynucleotide and Polypeptide Variants

[284] The invention also encompasses B7-like variants. The present invention is directed to variants of the polynucleotide sequence disclosed in SEQ ID NO:X or the complementary strand thereto, and/or the cDNA sequence contained in cDNA plasmid:V.

[285] The present invention also encompasses variants of the polypeptide sequence disclosed in SEQ ID NO:Y, a polypeptide sequence encoded by the polynucleotide sequence in SEQ ID NO:X and/or a polypeptide sequence encoded by the cDNA in cDNA plasmid:V.

[286] "Variant" refers to a polynucleotide or polypeptide differing from the polynucleotide or polypeptide of the present invention, but retaining properties thereof. Generally, variants are overall closely similar, and, in many regions, identical to the polynucleotide or polypeptide of the present invention.

[287] Thus, one aspect of the invention provides an isolated nucleic acid molecule comprising, or alternatively consisting of, a polynucleotide having a nucleotide sequence selected from the group consisting of: (a) a nucleotide sequence described in SEQ ID NO:X or contained in the cDNA sequence of Plasmid:V; (b) a nucleotide sequence in SEQ ID NO:X or the cDNA in Plasmid:V which encodes the complete amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in Plasmid:V; (c) a nucleotide sequence in SEQ ID NO:X or the cDNA in Plasmid:V which encodes a mature B7-like polypeptide; (d) a nucleotide sequence in SEQ ID NO:X or the cDNA sequence of Plasmid:V, which encodes a biologically active fragment of a B7-like polypeptide; (e) a nucleotide sequence in SEQ ID NO:X or the cDNA sequence of Plasmid:V, which encodes an antigenic fragment of a B7-like polypeptide; (f) a nucleotide sequence encoding a B7-like polypeptide comprising the complete amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in Plasmid:V; (g) a nucleotide sequence encoding a mature B7-like polypeptide of the amino acid sequence of SEQ ID NO:Y or the amino acid sequence encoded by the cDNA in Plasmid:V; (h) a nucleotide sequence encoding a biologically active fragment of a B7-like polypeptide having the complete amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in Plasmid:V; (i) a nucleotide sequence encoding an antigenic fragment of a B7-like polypeptide having the complete amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in Plasmid:V; and (j) a nucleotide sequence complementary to any of the nucleotide sequences in (a), (b), (c), (d), (e), (f), (g), (h), or (i) above.

[288] The present invention is also directed to nucleic acid molecules which comprise, or alternatively consist of, a nucleotide sequence which is at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100%, identical to, for example, any of the nucleotide sequences in (a), (b), (c), (d), (e), (f), (g), (h), (i), or (j) above, the nucleotide coding sequence in SEQ ID NO:X or the complementary strand thereto, the nucleotide coding sequence of the cDNA contained in Plasmid:V or the complementary strand thereto, a nucleotide sequence encoding

the polypeptide of SEQ ID NO:Y, a nucleotide sequence encoding a polypeptide sequence encoded by the nucleotide sequence in SEQ ID NO:X, a polypeptide sequence encoded by the complement of the polynucleotide sequence in SEQ ID NO:X, a nucleotide sequence encoding the polypeptide encoded by the cDNA contained in Plasmid:V, the nucleotide sequence in SEQ ID NO:X encoding the polypeptide sequence as defined in column 10 of Table 1 or the complementary strand thereto, nucleotide sequences encoding the polypeptide as defined in column 10 of Table 1 or the complementary strand thereto, and/or polynucleotide fragments of any of these nucleic acid molecules (e.g., those fragments described herein). Polynucleotides which hybridize to the complement of these nucleic acid molecules under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention, as are polypeptides encoded by these polynucleotides and nucleic acids.

[289] In a preferred embodiment, the invention encompasses nucleic acid molecules which comprise, or alternatively, consist of a polynucleotide which hybridizes under stringent hybridization conditions, or alternatively, under lower stringency conditions, to a polynucleotide in (a), (b), (c), (d), (e), (f), (g), (h), or (i), above, as are polypeptides encoded by these polynucleotides. In another preferred embodiment, polynucleotides which hybridize to the complement of these nucleic acid molecules under stringent hybridization conditions, or alternatively, under lower stringency conditions, are also encompassed by the invention, as are polypeptides encoded by these polynucleotides.

[290] In another embodiment, the invention provides a purified protein comprising, or alternatively consisting of, a polypeptide having an amino acid sequence selected from the group consisting of: (a) the complete amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in Plasmid:V; (b) the amino acid sequence of a mature form of a B7-like polypeptide having the amino acid sequence of SEQ ID NO:Y or the amino acid sequence encoded by the cDNA in Plasmid:V; (c) the amino acid sequence of a biologically active fragment of a B7-like polypeptide having the complete amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in Plasmid:V; and (d) the amino acid sequence of an antigenic fragment of a B7-like polypeptide having the complete amino acid sequence of SEQ ID NO:Y or the complete amino acid sequence encoded by the cDNA in Plasmid:V.

[291] The present invention is also directed to proteins which comprise, or alternatively consist of, an amino acid sequence which is at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100%, identical to, for example, any of the amino acid sequences in (a), (b), (c), or (d), above, the amino acid sequence shown in SEQ ID NO:Y, the amino acid sequence encoded by the cDNA contained in Plasmid:V, the amino acid sequence as defined in column 10 of Table 1, an amino acid sequence encoded by the nucleotide sequence in SEQ ID NO:X, and an amino acid sequence encoded by the complement of the polynucleotide sequence in SEQ ID NO:X. Fragments of these polypeptides are also provided (e.g., those fragments described herein). Further proteins encoded by polynucleotides which hybridize to the complement of the nucleic acid molecules encoding these amino acid sequences under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention, as are the polynucleotides encoding these proteins.

[292] By a nucleic acid having a nucleotide sequence at least, for example, 95% "identical" to a reference nucleotide sequence of the present invention, it is intended that the nucleotide sequence of the nucleic acid is identical to the reference sequence except that the nucleotide sequence may include up to five point mutations per each 100 nucleotides of the reference nucleotide sequence encoding the polypeptide. In other words, to obtain a nucleic acid having a nucleotide sequence at least 95% identical to a reference nucleotide sequence, up to 5% of the nucleotides in the reference sequence may be deleted or substituted with another nucleotide, or a number of nucleotides up to 5% of the total nucleotides in the reference sequence may be inserted into the reference sequence. The query sequence may be an entire sequence referred to in Table 1, the ORF (open reading frame), or any fragment specified as described herein.

[293] As a practical matter, whether any particular nucleic acid molecule or polypeptide is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to a nucleotide sequence of the present invention can be determined conventionally using known computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. 6:237-245 (1990)). In a sequence alignment the query and subject sequences are both DNA sequences. An RNA sequence can be compared by converting U's to T's. The result of said global sequence alignment is in

percent identity. Preferred parameters used in a FASTDB alignment of DNA sequences to calculate percent identiy are: Matrix=Unitary, k-tuple=4, Mismatch Penalty=1, Joining Penalty=30, Randomization Group Length=0, Cutoff Score=1, Gap Penalty=5, Gap Size Penalty 0.05, Window Size=500 or the lenght of the subject nucleotide sequence, whichever is shorter.

[294] If the subject sequence is shorter than the query sequence because of 5' or 3' deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for 5' and 3' truncations of the subject sequence when calculating percent identity. For subject sequences truncated at the 5' or 3' ends, relative to the query sequence, the percent identity is corrected by calculating the number of bases of the query sequence that are 5' and 3' of the subject sequence, which are not matched/aligned, as a percent of the total bases of the query sequence. Whether a nucleotide is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This corrected score is what is used for the purposes of the present invention. Only bases outside the 5' and 3' bases of the subject sequence, as displayed by the FASTDB alignment, which are not matched/aligned with the query sequence, are calculated for the purposes of manually adjusting the percent identity score.

[295] For example, a 90 base subject sequence is aligned to a 100 base query sequence to determine percent identity. The deletions occur at the 5' end of the subject sequence and therefore, the FASTDB alignment does not show a matched/alignment of the first 10 bases at 5' end. The 10 unpaired bases represent 10% of the sequence (number of bases at the 5' and 3' ends not matched/total number of bases in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 bases were perfectly matched the final percent identity would be 90%. In another example, a 90 base subject sequence is compared with a 100 base query sequence. This time the deletions are internal deletions so that there are no bases on the 5' or 3' of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only bases 5' and 3' of the subject sequence which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are to made for the purposes of the present invention.

[296] By a polypeptide having an amino acid sequence at least, for example, 95% "identical" to a query amino acid sequence of the present invention, it is intended that the amino acid sequence of the subject polypeptide is identical to the query sequence except that the subject polypeptide sequence may include up to five amino acid alterations per each 100 amino acids of the query amino acid sequence. In other words, to obtain a polypeptide having an amino acid sequence at least 95% identical to a query amino acid sequence, up to 5% of the amino acid residues in the subject sequence may be inserted, deleted, (indels) or substituted with another amino acid. These alterations of the reference sequence may occur at the amino or carboxy terminal positions of the reference amino acid sequence or anywhere between those terminal positions, interspersed either individually among residues in the reference sequence or in one or more contiguous groups within the reference sequence.

[297] As a practical matter, whether any particular polypeptide is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to, for instance, the amino acid sequence referred to in Table 1 or a fragment thereof, the amino acid sequence encoded by the nucleotide sequence in SEQ ID NO:X or a fragment thereof, or to the amino acid sequence encoded by the cDNA in cDNA plasmid:V, or a fragment thereof, can be determined conventionally using known computer programs. A preferred method for determing the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci.6:237- 245(1990)). In a sequence alignment the query and subject sequences are either both nucleotide sequences or both amino acid sequences. The result of said global sequence alignment is in percent identity. Preferred parameters used in a FASTDB amino acid alignment are: Matrix=PAM 0, k-tuple=2, Mismatch Penalty=1, Joining Penalty=20, Randomization Group Length=0, Cutoff Score=1, Window Size=sequence length, Gap Penalty=5, Gap Size Penalty=0.05, Window Size=500 or the length of the subject amino acid sequence, whichever is shorter.

[298] If the subject sequence is shorter than the query sequence due to N- or C-terminal deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for N- and C-terminal truncations of the subject sequence when calculating global percent identity. For subject sequences truncated at the N- and C-termini, relative to the query sequence, the percent identity is

corrected by calculating the number of residues of the query sequence that are N- and C-terminal of the subject sequence, which are not matched/aligned with a corresponding subject residue, as a percent of the total bases of the query sequence. Whether a residue is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This final percent identity score is what is used for the purposes of the present invention. Only residues to the N- and C-termini of the subject sequence, which are not matched/aligned with the query sequence, are considered for the purposes of manually adjusting the percent identity score. That is, only query residue positions outside the farthest N- and C- terminal residues of the subject sequence.

[299] For example, a 90 amino acid residue subject sequence is aligned with a 100 residue query sequence to determine percent identity. The deletion occurs at the N-terminus of the subject sequence and therefore, the FASTDB alignment does not show a matching/alignment of the first 10 residues at the N-terminus. The 10 unpaired residues represent 10% of the sequence (number of residues at the N- and C- termini not matched/total number of residues in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 residues were perfectly matched the final percent identity would be 90%. In another example, a 90 residue subject sequence is compared with a 100 residue query sequence. This time the deletions are internal deletions so there are no residues at the N- or C-termini of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only residue positions outside the N- and C-terminal ends of the subject sequence, as displayed in the FASTDB alignment, which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are to made for the purposes of the present invention.

[300] The variants may contain alterations in the coding regions, non-coding regions, or both. Especially preferred are polynucleotide variants containing alterations which produce silent substitutions, additions, or deletions, but do not alter the properties or activities of the encoded polypeptide. Nucleotide variants produced by silent substitutions due to the degeneracy of the genetic code are preferred. Moreover, variants in which less than 50, less than 40, less than 30, less than 20, less than 10, or 5-50, 5-25, 5-10, 1-5, or 1-2 amino acids

are substituted, deleted, or added in any combination are also preferred. Polynucleotide variants can be produced for a variety of reasons, e.g., to optimize codon expression for a particular host (change codons in the human mRNA to those preferred by a bacterial host such as E. coli).

[301] Naturally occurring variants are called "allelic variants," and refer to one of several alternate forms of a gene occupying a given locus on a chromosome of an organism. (Genes II, Lewin, B., ed., John Wiley & Sons, New York (1985)). These allelic variants can vary at either the polynucleotide and/or polypeptide level and are included in the present invention. Alternatively, non-naturally occurring variants may be produced by mutagenesis techniques or by direct synthesis.

[302] Using known methods of protein engineering and recombinant DNA technology, variants may be generated to improve or alter the characteristics of the polypeptides of the present invention. For instance, as discussed herein, one or more amino acids can be deleted from the N-terminus or C-terminus of the polypeptide of the present invention without substantial loss of biological function. The authors of Ron et al., J. Biol. Chem. 268: 2984-2988 (1993), reported variant KGF proteins having heparin binding activity even after deleting 3, 8, or 27 amino-terminal amino acid residues. Similarly, Interferon gamma exhibited up to ten times higher activity after deleting 8-10 amino acid residues from the carboxy terminus of this protein. (Dobeli et al., J. Biotechnology 7:199-216 (1988)).

[303] Moreover, ample evidence demonstrates that variants often retain a biological activity similar to that of the naturally occurring protein. For example, Gayle and coworkers (J. Biol. Chem 268:22105-22111 (1993)) conducted extensive mutational analysis of human cytokine IL-1a. They used random mutagenesis to generate over 3,500 individual IL-1a mutants that averaged 2.5 amino acid changes per variant over the entire length of the molecule. Multiple mutations were examined at every possible amino acid position. The investigators found that "[m]ost of the molecule could be altered with little effect on either [binding or biological activity]." (See, Abstract.) In fact, only 23 unique amino acid sequences, out of more than 3,500 nucleotide sequences examined, produced a protein that significantly differed in activity from wild-type.

[304] Furthermore, as discussed herein, even if deleting one or more amino acids from the N-terminus or C-terminus of a polypeptide results in modification or loss of one or more biological functions, other biological activities may still be retained. For example, the ability

of a deletion variant to induce and/or to bind antibodies which recognize the secreted form will likely be retained when less than the majority of the residues of the secreted form are removed from the N-terminus or C-terminus. Whether a particular polypeptide lacking N- or C-terminal residues of a protein retains such immunogenic activities can readily be determined by routine methods described herein and otherwise known in the art.

[305] Thus, the invention further includes polypeptide variants which show a functional activity (e.g. biological activity) of the polypeptide of the invention, of which they are a variant. Such variants include deletions, insertions, inversions, repeats, and substitutions selected according to general rules known in the art so as have little effect on activity.

[306] The present application is directed to nucleic acid molecules at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleic acid sequences disclosed herein, (e.g., encoding a polypeptide having the amino acid sequence of an N and/or C terminal deletion), irrespective of whether they encode a polypeptide having functional activity. This is because even where a particular nucleic acid molecule does not encode a polypeptide having functional activity, one of skill in the art would still know how to use the nucleic acid molecule, for instance, as a hybridization probe or a polymerase chain reaction (PCR) primer. Uses of the nucleic acid molecules of the present invention that do not encode a polypeptide having functional activity include, inter alia, (1) isolating a gene or allelic or splice variants thereof in a cDNA library; (2) in situ hybridization (e.g., "FISH") to metaphase chromosomal spreads to provide precise chromosomal location of the gene, as described in Verma et al., Human Chromosomes: A Manual of Basic Techniques, Pergamon Press, New York (1988); and (3) Northern Blot analysis for detecting mRNA expression in specific tissues.

[307] Preferred, however, are nucleic acid molecules having sequences at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleic acid sequences disclosed herein, which do, in fact, encode a polypeptide having functional activity of a polypeptide of the invention.

[308] Of course, due to the degeneracy of the genetic code, one of ordinary skill in the art will immediately recognize that a large number of the nucleic acid molecules having a sequence at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to, for example, the nucleic acid sequence of the cDNA in cDNA plasmid:V, the nucleic acid sequence referred to in Table 1 (SEQ ID NO:X), or fragments thereof, will encode

polypeptides "having functional activity." In fact, since degenerate variants of any of these nucleotide sequences all encode the same polypeptide, in many instances, this will be clear to the skilled artisan even without performing the above described comparison assay. It will be further recognized in the art that, for such nucleic acid molecules that are not degenerate variants, a reasonable number will also encode a polypeptide having functional activity. This is because the skilled artisan is fully aware of amino acid substitutions that are either less likely or not likely to significantly effect protein function (e.g., replacing one aliphatic amino acid with a second aliphatic amino acid), as further described below.

[309] For example, guidance concerning how to make phenotypically silent amino acid substitutions is provided in Bowie et al., "Deciphering the Message in Protein Sequences: Tolerance to Amino Acid Substitutions," Science 247:1306-1310 (1990), wherein the authors indicate that there are two main strategies for studying the tolerance of an amino acid sequence to change.

[310] The first strategy exploits the tolerance of amino acid substitutions by natural selection during the process of evolution. By comparing amino acid sequences in different species, conserved amino acids can be identified. These conserved amino acids are likely important for protein function. In contrast, the amino acid positions where substitutions have been tolerated by natural selection indicates that these positions are not critical for protein function. Thus, positions tolerating amino acid substitution could be modified while still maintaining biological activity of the protein.

[311] The second strategy uses genetic engineering to introduce amino acid changes at specific positions of a cloned gene to identify regions critical for protein function. For example, site directed mutagenesis or alanine-scanning mutagenesis (introduction of single alanine mutations at every residue in the molecule) can be used. (Cunningham and Wells, Science 244:1081-1085 (1989)). The resulting mutant molecules can then be tested for biological activity.

[312] As the authors state, these two strategies have revealed that proteins are surprisingly tolerant of amino acid substitutions. The authors further indicate which amino acid changes are likely to be permissive at certain amino acid positions in the protein. For example, most buried (within the tertiary structure of the protein) amino acid residues require nonpolar side chains, whereas few features of surface side chains are generally conserved. Moreover, tolerated conservative amino acid substitutions involve replacement of the

aliphatic or hydrophobic amino acids Ala, Val, Leu and Ile; replacement of the hydroxyl residues Ser and Thr; replacement of the acidic residues Asp and Glu; replacement of the amide residues Asn and Gln, replacement of the basic residues Lys, Arg, and His; replacement of the aromatic residues Phe, Tyr, and Trp, and replacement of the small-sized amino acids Ala, Ser, Thr, Met, and Gly. Besides conservative amino acid substitution, variants of the present invention include (i) substitutions with one or more of the non-conserved amino acid residues, where the substituted amino acid residues may or may not be one encoded by the genetic code, or (ii) substitution with one or more of amino acid residues having a substituent group, or (iii) fusion of the mature polypeptide with another compound, such as a compound to increase the stability and/or solubility of the polypeptide (for example, polyethylene glycol), or (iv) fusion of the polypeptide with additional amino acids, such as, for example, an IgG Fc fusion region peptide, or leader or secretory sequence, or a sequence facilitating purification or (v) fusion of the polypeptide with another compound, such as albumin (including but not limited to recombinant albumin (see, e.g., U.S. Patent No. 5,876,969, issued March 2, 1999, EP Patent 0 413 622, and U.S. Patent No. 5,766,883, issued June 16, 1998, herein incorporated by reference in their entirety)). Such variant polypeptides are deemed to be within the scope of those skilled in the art from the teachings herein.

[313] For example, polypeptide variants containing amino acid substitutions of charged amino acids with other charged or neutral amino acids may produce proteins with improved characteristics, such as less aggregation. Aggregation of pharmaceutical formulations both reduces activity and increases clearance due to the aggregate's immunogenic activity. (Pinckard et al., Clin. Exp. Immunol. 2:331-340 (1967); Robbins et al., Diabetes 36: 838-845 (1987); Cleland et al., Crit. Rev. Therapeutic Drug Carrier Systems 10:307-377 (1993)).

[314] A further embodiment of the invention relates to a polypeptide which comprises the amino acid sequence of a polypeptide having an amino acid sequence which contains at least one amino acid substitution, but not more than 50 amino acid substitutions, even more preferably, not more than 40 amino acid substitutions, still more preferably, not more than 30 amino acid substitutions, and still even more preferably, not more than 20 amino acid substitutions. Of course it is highly preferable for a polypeptide to have an amino acid sequence which comprises the amino acid sequence of a polypeptide of SEQ ID NO:Y, an amino acid sequence encoded by SEQ ID NO:X, and/or the amino acid sequence encoded by the cDNA in cDNA plasmid:V which contains, in order of ever-increasing preference, at least

one, but not more than 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 amino acid substitutions. In specific embodiments, the number of additions, substitutions, and/or deletions in the amino acid sequence of SEQ ID NO:Y or fragments thereof (e.g., the mature form and/or other fragments described herein), an amino acid sequence encoded by SEQ ID NO:X or fragments thereof, and/or the amino acid sequence encoded by cDNA plasmid:V or fragments thereof, is 1-5, 5-10, 5-25, 5-50, 10-50 or 50-150, conservative amino acid substitutions are preferable. As discussed herein, any polypeptide of the present invention can be used to generate fusion proteins. For example, the polypeptide of the present invention, when fused to a second protein, can be used as an antigenic tag. Antibodies raised against the polypeptide of the present invention can be used to indirectly detect the second protein by binding to the polypeptide. Moreover, because secreted proteins target cellular locations based on trafficking signals, polypeptides of the present invention which are shown to be secreted can be used as targeting molecules once fused to other proteins.

[315] Examples of domains that can be fused to polypeptides of the present invention include not only heterologous signal sequences, but also other heterologous functional regions. The fusion does not necessarily need to be direct, but may occur through linker sequences.

[316] In certain preferred embodiments, proteins of the invention comprise fusion proteins wherein the polypeptides are N and/or C- terminal deletion mutants. In preferred embodiments, the application is directed to nucleic acid molecules at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to the nucleic acid sequences encoding polypeptides having the amino acid sequence of the specific N- and C-terminal deletions mutants. Polynucleotides encoding these polypeptides, including fragments and/or variants, are also encompassed by the invention.

[317] Moreover, fusion proteins may also be engineered to improve characteristics of the polypeptide of the present invention. For instance, a region of additional amino acids, particularly charged amino acids, may be added to the N-terminus of the polypeptide to improve stability and persistence during purification from the host cell or subsequent handling and storage. Also, peptide moieties may be added to the polypeptide to facilitate purification. Such regions may be removed prior to final preparation of the polypeptide. The addition of peptide moieties to facilitate handling of polypeptides are familiar and routine techniques in the art.

[318] As one of skill in the art will appreciate, polypeptides of the present invention of the present invention and the epitope-bearing fragments thereof described above can be combined with heterologous polypeptide sequences. For example, the polypeptides of the present invention may be fused with heterologous polypeptide sequences, for example, the polypeptides of the present invention may be fused with the constant domain of immunoglobulins (IgA, IgE, IgG, IgM) or portions thereof (CH1, CH2, CH3, and any combination thereof, including both entire domains and portions thereof), resulting in chimeric polypeptides. These fusion proteins facilitate purification and show an increased half-life in vivo. One reported example describes chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. (EP A 394,827; Traunecker et al., Nature 331:84-86 (1988)). Fusion proteins having disulfide-linked dimeric structures (due to the IgG) can also be more efficient in binding and neutralizing other molecules, than the monomeric protein or protein fragment alone. (Fountoulakis et al., J. Biochem. 270:3958-3964 (1995)).

Vectors, Host Cells, and Protein Production

[319] The present invention also relates to vectors containing the polynucleotide of the present invention, host cells, and the production of polypeptides by recombinant techniques. The vector may be, for example, a phage, plasmid, viral, or retroviral vector. Retroviral vectors may be replication competent or replication defective. In the latter case, viral propagation generally will occur only in complementing host cells.

[320] The polynucleotides of the invention may be joined to a vector containing a selectable marker for propagation in a host. Generally, a plasmid vector is introduced in a precipitate, such as a calcium phosphate precipitate, or in a complex with a charged lipid. If the vector is a virus, it may be packaged in vitro using an appropriate packaging cell line and then transduced into host cells.

[321] The polynucleotide insert should be operatively linked to an appropriate promoter, such as the phage lambda PL promoter, the E. coli lac, trp, phoA and tac promoters, the SV40 early and late promoters and promoters of retroviral LTRs, to name a few. Other suitable promoters will be known to the skilled artisan. The expression constructs will further contain sites for transcription initiation, termination, and, in the transcribed region, a ribosome

binding site for translation. The coding portion of the transcripts expressed by the constructs will preferably include a translation initiating codon at the beginning and a termination codon (UAA, UGA or UAG) appropriately positioned at the end of the polypeptide to be translated.

[322] As indicated, the expression vectors will preferably include at least one selectable marker. Such markers include dihydrofolate reductase, G418 or neomycin resistance for eukaryotic cell culture and tetracycline, kanamycin or ampicillin resistance genes for culturing in E. coli and other bacteria. Representative examples of appropriate hosts include, but are not limited to, bacterial cells, such as E. coli, Streptomyces and Salmonella typhimurium cells; fungal cells, such as yeast cells (e.g., Saccharomyces cerevisiae or Pichia pastoris (ATCC Accession No. 201178)); insect cells such as Drosophila S2 and Spodoptera Sf9 cells; animal cells such as CHO, COS, 293, and Bowes melanoma cells; and plant cells. Appropriate culture mediums and conditions for the above-described host cells are known in the art.

[323] Among vectors preferred for use in bacteria include pQE70, pQE60 and pQE-9, available from QIAGEN, Inc.; pBluescript vectors, Phagescript vectors, pNH8A, pNH16a, pNH18A, pNH46A, available from Stratagene Cloning Systems, Inc.; and ptrc99a, pKK223-3, pKK233-3, pDR540, pRIT5 available from Pharmacia Biotech, Inc. Among preferred eukaryotic vectors are pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; and pSVK3, pBPV, pMSG and pSVL available from Pharmacia. Preferred expression vectors for use in yeast systems include, but are not limited to pYES2, pYD1, pTEF1/Zeo, pYES2/GS, pPICZ, pGAPZ, pGAPZalph, pPIC9, pPIC3.5, pHIL-D2, pHIL-S1, pPIC3.5K, pPIC9K, and PAO815 (all available from Invitrogen, Carlbad, CA). Other suitable vectors will be readily apparent to the skilled artisan.

[324] Introduction of the construct into the host cell can be effected by calcium phosphate transfection, DEAE-dextran mediated transfection, cationic lipid-mediated transfection, electroporation, transduction, infection, or other methods. Such methods are described in many standard laboratory manuals, such as Davis et al., Basic Methods In Molecular Biology (1986). It is specifically contemplated that the polypeptides of the present invention may in fact be expressed by a host cell lacking a recombinant vector.

[325] A polypeptide of this invention can be recovered and purified from recombinant cell cultures by well-known methods including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose

chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Most preferably, high performance liquid chromatography ("HPLC") is employed for purification.

[326] Polypeptides of the present invention can also be recovered from: products purified from natural sources, including bodily fluids, tissues and cells, whether directly isolated or cultured; products of chemical synthetic procedures; and products produced by recombinant techniques from a prokaryotic or eukaryotic host, including, for example, bacterial, yeast, higher plant, insect, and mammalian cells. Depending upon the host employed in a recombinant production procedure, the polypeptides of the present invention may be glycosylated or may be non-glycosylated. In addition, polypeptides of the invention may also include an initial modified methionine residue, in some cases as a result of host-mediated processes. Thus, it is well known in the art that the N-terminal methionine encoded by the translation initiation codon generally is removed with high efficiency from any protein after translation in all eukaryotic cells. While the N-terminal methionine on most proteins also is efficiently removed in most prokaryotes, for some proteins, this prokaryotic removal process is inefficient, depending on the nature of the amino acid to which the N-terminal methionine is covalently linked.

[327] In one embodiment, the yeast *Pichia pastoris* is used to express polypeptides of the invention in a eukaryotic system. *Pichia pastoris* is a methylotrophic yeast which can metabolize methanol as its sole carbon source. A main step in the methanol metabolization pathway is the oxidation of methanol to formaldehyde using O_2. This reaction is catalyzed by the enzyme alcohol oxidase. In order to metabolize methanol as its sole carbon source, *Pichia pastoris* must generate high levels of alcohol oxidase due, in part, to the relatively low affinity of alcohol oxidase for O_2. Consequently, in a growth medium depending on methanol as a main carbon source, the promoter region of one of the two alcohol oxidase genes (*AOX1*) is highly active. In the presence of methanol, alcohol oxidase produced from the *AOX1* gene comprises up to approximately 30% of the total soluble protein in *Pichia pastoris*. *See*, Ellis, S.B., *et al., Mol. Cell. Biol.* 5:1111-21 (1985); Koutz, P.J, *et al., Yeast* 5:167-77 (1989); Tschopp, J.F., *et al., Nucl. Acids Res.* 15:3859-76 (1987). Thus, a heterologous coding sequence, such as, for example, a polynucleotide of the present

invention, under the transcriptional regulation of all or part of the *AOX1* regulatory sequence is expressed at exceptionally high levels in *Pichia* yeast grown in the presence of methanol.

[328] In one example, the plasmid vector pPIC9K is used to express DNA encoding a polypeptide of the invention, as set forth herein, in a *Pichea* yeast system essentially as described in "*Pichia* Protocols: Methods in Molecular Biology," D.R. Higgins and J. Cregg, eds. The Humana Press, Totowa, NJ, 1998. This expression vector allows expression and secretion of a polypeptide of the invention by virtue of the strong *AOX1* promoter linked to the *Pichia pastoris* alkaline phosphatase (PHO) secretory signal peptide (i.e., leader) located upstream of a multiple cloning site.

[329] Many other yeast vectors could be used in place of pPIC9K, such as, pYES2, pYD1, pTEF1/Zeo, pYES2/GS, pPICZ, pGAPZ, pGAPZalpha, pPIC9, pPIC3.5, pHIL-D2, pHIL-S1, pPIC3.5K, and PAO815, as one skilled in the art would readily appreciate, as long as the proposed expression construct provides appropriately located signals for transcription, translation, secretion (if desired), and the like, including an in-frame AUG as required.

[330] In another embodiment, high-level expression of a heterologous coding sequence, such as, for example, a polynucleotide of the present invention, may be achieved by cloning the heterologous polynucleotide of the invention into an expression vector such as, for example, pGAPZ or pGAPZalpha, and growing the yeast culture in the absence of methanol.

[331] In addition to encompassing host cells containing the vector constructs discussed herein, the invention also encompasses primary, secondary, and immortalized host cells of vertebrate origin, particularly mammalian origin, that have been engineered to delete or replace endogenous genetic material (e.g., coding sequence), and/or to include genetic material (e.g., heterologous polynucleotide sequences) that is operably associated with polynucleotides of the invention, and which activates, alters, and/or amplifies endogenous polynucleotides. For example, techniques known in the art may be used to operably associate heterologous control regions (e.g., promoter and/or enhancer) and endogenous polynucleotide sequences via homologous recombination (see, e.g., U.S. Patent No. 5,641,670, issued June 24, 1997; International Publication No. WO 96/29411, published September 26, 1996; International Publication No. WO 94/12650, published August 4, 1994; Koller et al., Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); and Zijlstra et al., Nature

342:435-438 (1989), the disclosures of each of which are incorporated by reference in their entireties).

[332] In addition, polypeptides of the invention can be chemically synthesized using techniques known in the art (e.g., see Creighton, 1983, Proteins: Structures and Molecular Principles, W.H. Freeman & Co., N.Y., and Hunkapiller et al., *Nature*, 310:105-111 (1984)). For example, a polypeptide corresponding to a fragment of a polypeptide can be synthesized by use of a peptide synthesizer. Furthermore, if desired, nonclassical amino acids or chemical amino acid analogs can be introduced as a substitution or addition into the polypeptide sequence. Non-classical amino acids include, but are not limited to, to the D-isomers of the common amino acids, 2,4-diaminobutyric acid, a-amino isobutyric acid, 4-aminobutyric acid, Abu, 2-amino butyric acid, g-Abu, e-Ahx, 6-amino hexanoic acid, Aib, 2-amino isobutyric acid, 3-amino propionic acid, ornithine, norleucine, norvaline, hydroxyproline, sarcosine, citrulline, homocitrulline, cysteic acid, t-butylglycine, t-butylalanine, phenylglycine, cyclohexylalanine, b-alanine, fluoro-amino acids, designer amino acids such as b-methyl amino acids, Ca-methyl amino acids, Na-methyl amino acids, and amino acid analogs in general. Furthermore, the amino acid can be D (dextrorotary) or L (levorotary).

[333] The invention encompasses polypeptides of the present invention which are differentially modified during or after translation, e.g., by glycosylation, acetylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to an antibody molecule or other cellular ligand, etc. Any of numerous chemical modifications may be carried out by known techniques, including but not limited, to specific chemical cleavage by cyanogen bromide, trypsin, chymotrypsin, papain, V8 protease, $NaBH_4$; acetylation, formylation, oxidation, reduction; metabolic synthesis in the presence of tunicamycin; etc.

[334] Additional post-translational modifications encompassed by the invention include, for example, e.g., N-linked or O-linked carbohydrate chains, processing of N-terminal or C-terminal ends), attachment of chemical moieties to the amino acid backbone, chemical modifications of N-linked or O-linked carbohydrate chains, and addition or deletion of an N-terminal methionine residue as a result of procaryotic host cell expression. The polypeptides may also be modified with a detectable label, such as an enzymatic, fluorescent, isotopic or affinity label to allow for detection and isolation of the protein.

[335] Also provided by the invention are chemically modified derivatives of the polypeptides of the invention which may provide additional advantages such as increased solubility, stability and circulating time of the polypeptide, or decreased immunogenicity (see U.S. Patent No. 4,179,337). The chemical moieties for derivitization may be selected from water soluble polymers such as polyethylene glycol, ethylene glycol/propylene glycol copolymers, carboxymethylcellulose, dextran, polyvinyl alcohol and the like. The polypeptides may be modified at random positions within the molecule, or at predetermined positions within the molecule and may include one, two, three or more attached chemical moieties.

[336] The polymer may be of any molecular weight, and may be branched or unbranched. For polyethylene glycol, the preferred molecular weight is between about 1 kDa and about 100 kDa (the term "about" indicating that in preparations of polyethylene glycol, some molecules will weigh more, some less, than the stated molecular weight) for ease in handling and manufacturing. Other sizes may be used, depending on the desired therapeutic profile (e.g., the duration of sustained release desired, the effects, if any on biological activity, the ease in handling, the degree or lack of antigenicity and other known effects of the polyethylene glycol to a therapeutic protein or analog).

[337] The polyethylene glycol molecules (or other chemical moieties) should be attached to the protein with consideration of effects on functional or antigenic domains of the protein. There are a number of attachment methods available to those skilled in the art, e.g., EP 0 401 384, herein incorporated by reference (coupling PEG to G-CSF), see also Malik et al., Exp. Hematol. 20:1028-1035 (1992) (reporting pegylation of GM-CSF using tresyl chloride). For example, polyethylene glycol may be covalently bound through amino acid residues via a reactive group, such as, a free amino or carboxyl group. Reactive groups are those to which an activated polyethylene glycol molecule may be bound. The amino acid residues having a free amino group may include lysine residues and the N-terminal amino acid residues; those having a free carboxyl group may include aspartic acid residues glutamic acid residues and the C-terminal amino acid residue. Sulfhydryl groups may also be used as a reactive group for attaching the polyethylene glycol molecules. Preferred for therapeutic purposes is attachment at an amino group, such as attachment at the N-terminus or lysine group.

[338] One may specifically desire proteins chemically modified at the N-terminus. Using polyethylene glycol as an illustration of the present composition, one may select from

a variety of polyethylene glycol molecules (by molecular weight, branching, etc.), the proportion of polyethylene glycol molecules to protein (polypeptide) molecules in the reaction mix, the type of pegylation reaction to be performed, and the method of obtaining the selected N-terminally pegylated protein. The method of obtaining the N-terminally pegylated preparation (i.e., separating this moiety from other monopegylated moieties if necessary) may be by purification of the N-terminally pegylated material from a population of pegylated protein molecules. Selective proteins chemically modified at the N-terminus modification may be accomplished by reductive alkylation which exploits differential reactivity of different types of primary amino groups (lysine versus the N-terminal) available for derivatization in a particular protein. Under the appropriate reaction conditions, substantially selective derivatization of the protein at the N-terminus with a carbonyl group containing polymer is achieved.

[339] The polypeptides of the invention may be in monomers or multimers (i.e., dimers, trimers, tetramers and higher multimers). Accordingly, the present invention relates to monomers and multimers of the polypeptides of the invention, their preparation, and compositions (preferably, Therapeutics) containing them. In specific embodiments, the polypeptides of the invention are monomers, dimers, trimers or tetramers. In additional embodiments, the multimers of the invention are at least dimers, at least trimers, or at least tetramers.

[340] Multimers encompassed by the invention may be homomers or heteromers. As used herein, the term homomer, refers to a multimer containing only polypeptides corresponding to the amino acid sequence of SEQ ID NO:Y or an amino acid sequence encoded by SEQ ID NO:X or the complement of SEQ ID NO:X, and/or an amino acid sequence encoded by cDNA Plasmid:V (including fragments, variants, splice variants, and fusion proteins, corresponding to these as described herein). These homomers may contain polypeptides having identical or different amino acid sequences. In a specific embodiment, a homomer of the invention is a multimer containing only polypeptides having an identical amino acid sequence. In another specific embodiment, a homomer of the invention is a multimer containing polypeptides having different amino acid sequences. In specific embodiments, the multimer of the invention is a homodimer (e.g., containing polypeptides having identical or different amino acid sequences) or a homotrimer (e.g., containing polypeptides having identical and/or different amino acid sequences). In additional

embodiments, the homomeric multimer of the invention is at least a homodimer, at least a homotrimer, or at least a homotetramer.

[341] As used herein, the term heteromer refers to a multimer containing one or more heterologous polypeptides (i.e., polypeptides of different proteins) in addition to the polypeptides of the invention. In a specific embodiment, the multimer of the invention is a heterodimer, a heterotrimer, or a heterotetramer. In additional embodiments, the heteromeric multimer of the invention is at least a heterodimer, at least a heterotrimer, or at least a heterotetramer.

[342] Multimers of the invention may be the result of hydrophobic, hydrophilic, ionic and/or covalent associations and/or may be indirectly linked, by for example, liposome formation. Thus, in one embodiment, multimers of the invention, such as, for example, homodimers or homotrimers, are formed when polypeptides of the invention contact one another in solution. In another embodiment, heteromultimers of the invention, such as, for example, heterotrimers or heterotetramers, are formed when polypeptides of the invention contact antibodies to the polypeptides of the invention (including antibodies to the heterologous polypeptide sequence in a fusion protein of the invention) in solution. In other embodiments, multimers of the invention are formed by covalent associations with and/or between the polypeptides of the invention. Such covalent associations may involve one or more amino acid residues contained in the polypeptide sequence (e.g., that recited in SEQ ID NO:Y, or contained in a polypeptide encoded by SEQ ID NO:X, and/or the cDNA plasmid:V). In one instance, the covalent associations are cross-linking between cysteine residues located within the polypeptide sequences which interact in the native (i.e., naturally occurring) polypeptide. In another instance, the covalent associations are the consequence of chemical or recombinant manipulation. Alternatively, such covalent associations may involve one or more amino acid residues contained in the heterologous polypeptide sequence in a fusion protein. In one example, covalent associations are between the heterologous sequence contained in a fusion protein of the invention (see, e.g., US Patent Number 5,478,925). In a specific example, the covalent associations are between the heterologous sequence contained in a Fc fusion protein of the invention (as described herein). In another specific example, covalent associations of fusion proteins of the invention are between heterologous polypeptide sequence from another protein that is capable of forming covalently associated multimers, such as for example, osteoprotegerin (see, e.g., International

Publication NO: WO 98/49305, the contents of which are herein incorporated by reference in its entirety). In another embodiment, two or more polypeptides of the invention are joined through peptide linkers. Examples include those peptide linkers described in U.S. Pat. No. 5,073,627 (hereby incorporated by reference). Proteins comprising multiple polypeptides of the invention separated by peptide linkers may be produced using conventional recombinant DNA technology.

[343] Another method for preparing multimer polypeptides of the invention involves use of polypeptides of the invention fused to a leucine zipper or isoleucine zipper polypeptide sequence. Leucine zipper and isoleucine zipper domains are polypeptides that promote multimerization of the proteins in which they are found. Leucine zippers were originally identified in several DNA-binding proteins (Landschulz et al., Science 240:1759, (1988)), and have since been found in a variety of different proteins. Among the known leucine zippers are naturally occurring peptides and derivatives thereof that dimerize or trimerize. Examples of leucine zipper domains suitable for producing soluble multimeric proteins of the invention are those described in PCT application WO 94/10308, hereby incorporated by reference. Recombinant fusion proteins comprising a polypeptide of the invention fused to a polypeptide sequence that dimerizes or trimerizes in solution are expressed in suitable host cells, and the resulting soluble multimeric fusion protein is recovered from the culture supernatant using techniques known in the art.

[344] Trimeric polypeptides of the invention may offer the advantage of enhanced biological activity. Preferred leucine zipper moieties and isoleucine moieties are those that preferentially form trimers. One example is a leucine zipper derived from lung surfactant protein D (SPD), as described in Hoppe et al. (FEBS Letters 344:191, (1994)) and in U.S. patent application Ser. No. 08/446,922, hereby incorporated by reference. Other peptides derived from naturally occurring trimeric proteins may be employed in preparing trimeric polypeptides of the invention.

[345] In another example, proteins of the invention are associated by interactions between Flag® polypeptide sequence contained in fusion proteins of the invention containing Flag® polypeptide seuqence. In a further embodiment, associations proteins of the invention are associated by interactions between heterologous polypeptide sequence contained in Flag® fusion proteins of the invention and anti-Flag® antibody.

[346] The multimers of the invention may be generated using chemical techniques known in the art. For example, polypeptides desired to be contained in the multimers of the invention may be chemically cross-linked using linker molecules and linker molecule length optimization techniques known in the art (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Additionally, multimers of the invention may be generated using techniques known in the art to form one or more inter-molecule cross-links between the cysteine residues located within the sequence of the polypeptides desired to be contained in the multimer (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Further, polypeptides of the invention may be routinely modified by the addition of cysteine or biotin to the C-terminus or N-terminus of the polypeptide and techniques known in the art may be applied to generate multimers containing one or more of these modified polypeptides (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Additionally, techniques known in the art may be applied to generate liposomes containing the polypeptide components desired to be contained in the multimer of the invention (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety).

[347] Alternatively, multimers of the invention may be generated using genetic engineering techniques known in the art. In one embodiment, polypeptides contained in multimers of the invention are produced recombinantly using fusion protein technology described herein or otherwise known in the art (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). In a specific embodiment, polynucleotides coding for a homodimer of the invention are generated by ligating a polynucleotide sequence encoding a polypeptide of the invention to a sequence encoding a linker polypeptide and then further to a synthetic polynucleotide encoding the translated product of the polypeptide in the reverse orientation from the original C-terminus to the N-terminus (lacking the leader sequence) (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). In another embodiment, recombinant techniques described herein or otherwise known in the art are applied to generate recombinant polypeptides of the invention which contain a transmembrane domain (or hyrophobic or signal peptide) and which can be incorporated by membrane reconstitution techniques into liposomes (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety).

Antibodies

[348] Further polypeptides of the invention relate to antibodies and T-cell antigen receptors (TCR) which immunospecifically bind a polypeptide, polypeptide fragment, or variant of SEQ ID NO:Y, and/or an epitope, of the present invention (as determined by immunoassays well known in the art for assaying specific antibody-antigen binding). Antibodies of the invention include, but are not limited to, polyclonal, monoclonal, multispecific, human, humanized or chimeric antibodies, single chain antibodies, Fab fragments, F(ab') fragments, fragments produced by a Fab expression library, anti-idiotypic (anti-Id) antibodies (including, e.g., anti-Id antibodies to antibodies of the invention), and epitope-binding fragments of any of the above. The term "antibody," as used herein, refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, i.e., molecules that contain an antigen binding site that immunospecifically binds an antigen. The immunoglobulin molecules of the invention can be of any type (e.g., IgG, IgE, IgM, IgD, IgA and IgY), class (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass of immunoglobulin molecule.

[349] Most preferably the antibodies are human antigen-binding antibody fragments of the present invention and include, but are not limited to, Fab, Fab' and F(ab')2, Fd, single-chain Fvs (scFv), single-chain antibodies, disulfide-linked Fvs (sdFv) and fragments comprising either a VL or VH domain. Antigen-binding antibody fragments, including single-chain antibodies, may comprise the variable region(s) alone or in combination with the entirety or a portion of the following: hinge region, CH1, CH2, and CH3 domains. Also included in the invention are antigen-binding fragments also comprising any combination of variable region(s) with a hinge region, CH1, CH2, and CH3 domains. The antibodies of the invention may be from any animal origin including birds and mammals. Preferably, the antibodies are human, murine (e.g., mouse and rat), donkey, ship rabbit, goat, guinea pig, camel, horse, or chicken. As used herein, "human" antibodies include antibodies having the amino acid sequence of a human immunoglobulin and include antibodies isolated from human immunoglobulin libraries or from animals transgenic for one or more human immunoglobulin and that do not express endogenous immunoglobulins, as described infra and, for example in, U.S. Patent No. 5,939,598 by Kucherlapati et al.

[350] The antibodies of the present invention may be monospecific, bispecific, trispecific or of greater multispecificity. Multispecific antibodies may be specific for different epitopes of a polypeptide of the present invention or may be specific for both a polypeptide of the present invention as well as for a heterologous epitope, such as a heterologous polypeptide or solid support material. See, e.g., PCT publications WO 93/17715; WO 92/08802; WO 91/00360; WO 92/05793; Tutt, et al., J. Immunol. 147:60-69 (1991); U.S. Patent Nos. 4,474,893; 4,714,681; 4,925,648; 5,573,920; 5,601,819; Kostelny et al., J. Immunol. 148:1547-1553 (1992).

[351] Antibodies of the present invention may be described or specified in terms of the epitope(s) or portion(s) of a polypeptide of the present invention which they recognize or specifically bind. The epitope(s) or polypeptide portion(s) may be specified as described herein, e.g., by N-terminal and C-terminal positions, or by size in contiguous amino acid residues. Antibodies which specifically bind any epitope or polypeptide of the present invention may also be excluded. Therefore, the present invention includes antibodies that specifically bind polypeptides of the present invention, and allows for the exclusion of the same.

[352] Antibodies of the present invention may also be described or specified in terms of their cross-reactivity. Antibodies that do not bind any other analog, ortholog, or homolog of a polypeptide of the present invention are included. Antibodies that bind polypeptides with at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 65%, at least 60%, at least 55%, and at least 50% identity (as calculated using methods known in the art and described herein) to a polypeptide of the present invention are also included in the present invention. In specific embodiments, antibodies of the present invention cross-react with murine, rat and/or rabbit homologs of human proteins and the corresponding epitopes thereof. Antibodies that do not bind polypeptides with less than 95%, less than 90%, less than 85%, less than 80%, less than 75%, less than 70%, less than 65%, less than 60%, less than 55%, and less than 50% identity (as calculated using methods known in the art and described herein) to a polypeptide of the present invention are also included in the present invention. In a specific embodiment, the above-described cross-reactivity is with respect to any single specific antigenic or immunogenic polypeptide, or combination(s) of 2, 3, 4, 5, or more of the specific antigenic and/or immunogenic polypeptides disclosed herein. Further included in the present invention are antibodies which bind polypeptides encoded by polynucleotides which

hybridize to a polynucleotide of the present invention under stringent hybridization conditions (as described herein). Antibodies of the present invention may also be described or specified in terms of their binding affinity to a polypeptide of the invention. Preferred binding affinities include those with a dissociation constant or Kd less than 5 X 10^{-2} M, 10^{-2} M, 5 X 10^{-3} M, 10^{-3} M, 5 X 10^{-4} M, 10^{-4} M, 5 X 10^{-5} M, 10^{-5} M, 5 X 10^{-6} M, 10^{-6}M, 5 X 10^{-7} M, 10^{-7} M, 5 X 10^{-8} M, 10^{-8} M, 5 X 10^{-9} M, 10^{-9} M, 5 X 10^{-10} M, 10^{-10} M, 5 X 10^{-11} M, 10^{-11} M, 5 X 10^{-12} M, 10^{-12} M, 5 X 10^{-13} M, 10^{-13} M, 5 X 10^{-14} M, 10^{-14} M, 5 X 10^{-15} M, or 10^{-15} M.

[353] The invention also provides antibodies that competitively inhibit binding of an antibody to an epitope of the invention as determined by any method known in the art for determining competitive binding, for example, the immunoassays described herein. In preferred embodiments, the antibody competitively inhibits binding to the epitope by at least 95%, at least 90%, at least 85 %, at least 80%, at least 75%, at least 70%, at least 60%, or at least 50%.

[354] Antibodies of the present invention may act as agonists or antagonists of the polypeptides of the present invention. For example, the present invention includes antibodies which disrupt the receptor/ligand interactions with the polypeptides of the invention either partially or fully. Preferrably, antibodies of the present invention bind an antigenic epitope disclosed herein, or a portion thereof. The invention features both receptor-specific antibodies and ligand-specific antibodies. The invention also features receptor-specific antibodies which do not prevent ligand binding but prevent receptor activation. Receptor activation (i.e., signaling) may be determined by techniques described herein or otherwise known in the art. For example, receptor activation can be determined by detecting the phosphorylation (e.g., tyrosine or serine/threonine) of the receptor or its substrate by immunoprecipitation followed by western blot analysis (for example, as described supra). In specific embodiments, antibodies are provided that inhibit ligand activity or receptor activity by at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 60%, or at least 50% of the activity in absence of the antibody.

[355] The invention also features receptor-specific antibodies which both prevent ligand binding and receptor activation as well as antibodies that recognize the receptor-ligand complex, and, preferably, do not specifically recognize the unbound receptor or the unbound ligand. Likewise, included in the invention are neutralizing antibodies which bind the ligand and prevent binding of the ligand to the receptor, as well as antibodies which bind the ligand,

thereby preventing receptor activation, but do not prevent the ligand from binding the receptor. Further included in the invention are antibodies which activate the receptor. These antibodies may act as receptor agonists, i.e., potentiate or activate either all or a subset of the biological activities of the ligand-mediated receptor activation, for example, by inducing dimerization of the receptor. The antibodies may be specified as agonists, antagonists or inverse agonists for biological activities comprising the specific biological activities of the peptides of the invention disclosed herein. The above antibody agonists can be made using methods known in the art. See, e.g., PCT publication WO 96/40281; U.S. Patent No. 5,811,097; Deng et al., Blood 92(6):1981-1988 (1998); Chen et al., Cancer Res. 58(16):3668-3678 (1998); Harrop et al., J. Immunol. 161(4):1786-1794 (1998); Zhu et al., Cancer Res. 58(15):3209-3214 (1998); Yoon et al., J. Immunol. 160(7):3170-3179 (1998); Prat et al., J. Cell. Sci. 111(Pt2):237-247 (1998); Pitard et al., J. Immunol. Methods 205(2):177-190 (1997); Liautard et al., Cytokine 9(4):233-241 (1997); Carlson et al., J. Biol. Chem. 272(17):11295-11301 (1997); Taryman et al., Neuron 14(4):755-762 (1995); Muller et al., Structure 6(9):1153-1167 (1998); Bartunek et al., Cytokine 8(1):14-20 (1996) (which are all incorporated by reference herein in their entireties).

[356] Antibodies of the present invention may be used, for example, but not limited to, to purify, detect, and target the polypeptides of the present invention, including both in vitro and in vivo diagnostic and therapeutic methods. For example, the antibodies have use in immunoassays for qualitatively and quantitatively measuring levels of the polypeptides of the present invention in biological samples. See, e.g., Harlow et al., Antibodies: A Laboratory Manual, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988) (incorporated by reference herein in its entirety).

[357] As discussed in more detail below, the antibodies of the present invention may be used either alone or in combination with other compositions. The antibodies may further be recombinantly fused to a heterologous polypeptide at the N- or C-terminus or chemically conjugated (including covalently and non-covalently conjugations) to polypeptides or other compositions. For example, antibodies of the present invention may be recombinantly fused or conjugated to molecules useful as labels in detection assays and effector molecules such as heterologous polypeptides, drugs, radionuclides, or toxins. See, e.g., PCT publications WO 92/08495; WO 91/14438; WO 89/12624; U.S. Patent No. 5,314,995; and EP 396,387.

[358] The antibodies of the invention include derivatives that are modified, i.e, by the covalent attachment of any type of molecule to the antibody such that covalent attachment does not prevent the antibody from generating an anti-idiotypic response. For example, but not by way of limitation, the antibody derivatives include antibodies that have been modified, e.g., by glycosylation, acetylation, pegylation, phosphylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, etc. Any of numerous chemical modifications may be carried out by known techniques, including, but not limited to specific chemical cleavage, acetylation, formylation, metabolic synthesis of tunicamycin, etc. Additionally, the derivative may contain one or more non-classical amino acids.

[359] The antibodies of the present invention may be generated by any suitable method known in the art. Polyclonal antibodies to an antigen-of- interest can be produced by various procedures well known in the art. For example, a polypeptide of the invention can be administered to various host animals including, but not limited to, rabbits, mice, rats, etc. to induce the production of sera containing polyclonal antibodies specific for the antigen. Various adjuvants may be used to increase the immunological response, depending on the host species, and include but are not limited to, Freund's (complete and incomplete), mineral gels such as aluminum hydroxide, surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, keyhole limpet hemocyanins, dinitrophenol, and potentially useful human adjuvants such as BCG (bacille Calmette-Guerin) and corynebacterium parvum. Such adjuvants are also well known in the art.

[360] Monoclonal antibodies can be prepared using a wide variety of techniques known in the art including the use of hybridoma, recombinant, and phage display technologies, or a combination thereof. For example, monoclonal antibodies can be produced using hybridoma techniques including those known in the art and taught, for example, in Harlow et al., Antibodies: A Laboratory Manual, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988); Hammerling, et al., in: Monoclonal Antibodies and T-Cell Hybridomas 563-681 (Elsevier, N.Y., 1981) (said references incorporated by reference in their entireties). The term "monoclonal antibody" as used herein is not limited to antibodies produced through hybridoma technology. The term "monoclonal antibody" refers to an antibody that is derived from a single clone, including any eukaryotic, prokaryotic, or phage clone, and not the method by which it is produced.

[361] Methods for producing and screening for specific antibodies using hybridoma technology are routine and well known in the art and are discussed in detail in the Examples. In a non-limiting example, mice can be immunized with a polypeptide of the invention or a cell expressing such peptide. Once an immune response is detected, e.g., antibodies specific for the antigen are detected in the mouse serum, the mouse spleen is harvested and splenocytes isolated. The splenocytes are then fused by well known techniques to any suitable myeloma cells, for example cells from cell line SP20 available from the ATCC. Hybridomas are selected and cloned by limited dilution. The hybridoma clones are then assayed by methods known in the art for cells that secrete antibodies capable of binding a polypeptide of the invention. Ascites fluid, which generally contains high levels of antibodies, can be generated by immunizing mice with positive hybridoma clones.

[362] Accordingly, the present invention provides methods of generating monoclonal antibodies as well as antibodies produced by the method comprising culturing a hybridoma cell secreting an antibody of the invention wherein, preferably, the hybridoma is generated by fusing splenocytes isolated from a mouse immunized with an antigen of the invention with myeloma cells and then screening the hybridomas resulting from the fusion for hybridoma clones that secrete an antibody able to bind a polypeptide of the invention.

[363] Antibody fragments which recognize specific epitopes may be generated by known techniques. For example, Fab and F(ab')2 fragments of the invention may be produced by proteolytic cleavage of immunoglobulin molecules, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')2 fragments). F(ab')2 fragments contain the variable region, the light chain constant region and the CH1 domain of the heavy chain.

[364] For example, the antibodies of the present invention can also be generated using various phage display methods known in the art. In phage display methods, functional antibody domains are displayed on the surface of phage particles which carry the polynucleotide sequences encoding them. In a particular embodiment, such phage can be utilized to display antigen binding domains expressed from a repertoire or combinatorial antibody library (e.g., human or murine). Phage expressing an antigen binding domain that binds the antigen of interest can be selected or identified with antigen, e.g., using labeled antigen or antigen bound or captured to a solid surface or bead. Phage used in these methods are typically filamentous phage including fd and M13 binding domains expressed from phage with Fab, Fv or disulfide stabilized Fv antibody domains recombinantly fused to either the

phage gene III or gene VIII protein. Examples of phage display methods that can be used to make the antibodies of the present invention include those disclosed in Brinkman et al., J. Immunol. Methods 182:41-50 (1995); Ames et al., J. Immunol. Methods 184:177-186 (1995); Kettleborough et al., Eur. J. Immunol. 24:952-958 (1994); Persic et al., Gene 187 9-18 (1997); Burton et al., Advances in Immunology 57:191-280 (1994); PCT application No. PCT/GB91/01134; PCT publications WO 90/02809; WO 91/10737; WO 92/01047; WO 92/18619; WO 93/11236; WO 95/15982; WO 95/20401; and U.S. Patent Nos. 5,698,426; 5,223,409; 5,403,484; 5,580,717; 5,427,908; 5,750,753; 5,821,047; 5,571,698; 5,427,908; 5,516,637; 5,780,225; 5,658,727; 5,733,743 and 5,969,108; each of which is incorporated herein by reference in its entirety.

[365] As described in the above references, after phage selection, the antibody coding regions from the phage can be isolated and used to generate whole antibodies, including human antibodies, or any other desired antigen binding fragment, and expressed in any desired host, including mammalian cells, insect cells, plant cells, yeast, and bacteria, e.g., as described in detail below. For example, techniques to recombinantly produce Fab, Fab' and F(ab')2 fragments can also be employed using methods known in the art such as those disclosed in PCT publication WO 92/22324; Mullinax et al., BioTechniques 12(6):864-869 (1992); and Sawai et al., AJRI 34:26-34 (1995); and Better et al., Science 240:1041-1043 (1988) (said references incorporated by reference in their entireties).

[366] Examples of techniques which can be used to produce single-chain Fvs and antibodies include those described in U.S. Patents 4,946,778 and 5,258,498; Huston et al., Methods in Enzymology 203:46-88 (1991); Shu et al., PNAS 90:7995-7999 (1993); and Skerra et al., Science 240:1038-1040 (1988). For some uses, including in vivo use of antibodies in humans and in vitro detection assays, it may be preferable to use chimeric, humanized, or human antibodies. A chimeric antibody is a molecule in which different portions of the antibody are derived from different animal species, such as antibodies having a variable region derived from a murine monoclonal antibody and a human immunoglobulin constant region. Methods for producing chimeric antibodies are known in the art. See e.g., Morrison, Science 229:1202 (1985); Oi et al., BioTechniques 4:214 (1986); Gillies et al., (1989) J. Immunol. Methods 125:191-202; U.S. Patent Nos. 5,807,715; 4,816,567; and 4,816397, which are incorporated herein by reference in their entirety. Humanized antibodies are antibody molecules from non-human species antibody that binds the desired

antigen having one or more complementarity determining regions (CDRs) from the non-human species and a framework regions from a human immunoglobulin molecule. Often, framework residues in the human framework regions will be substituted with the corresponding residue from the CDR donor antibody to alter, preferably improve, antigen binding. These framework substitutions are identified by methods well known in the art, e.g., by modeling of the interactions of the CDR and framework residues to identify framework residues important for antigen binding and sequence comparison to identify unusual framework residues at particular positions. (See, e.g., Queen et al., U.S. Patent No. 5,585,089; Riechmann et al., Nature 332:323 (1988), which are incorporated herein by reference in their entireties.) Antibodies can be humanized using a variety of techniques known in the art including, for example, CDR-grafting (EP 239,400; PCT publication WO 91/09967; U.S. Patent Nos. 5,225,539; 5,530,101; and 5,585,089), veneering or resurfacing (EP 592,106; EP 519,596; Padlan, Molecular Immunology 28(4/5):489-498 (1991); Studnicka et al., Protein Engineering 7(6):805-814 (1994); Roguska. et al., PNAS 91:969-973 (1994)), and chain shuffling (U.S. Patent No. 5,565,332).

[367] Completely human antibodies are particularly desirable for therapeutic treatment of human patients. Human antibodies can be made by a variety of methods known in the art including phage display methods described above using antibody libraries derived from human immunoglobulin sequences. See also, U.S. Patent Nos. 4,444,887 and 4,716,111; and PCT publications WO 98/46645, WO 98/50433, WO 98/24893, WO 98/16654, WO 96/34096, WO 96/33735, and WO 91/10741; each of which is incorporated herein by reference in its entirety.

[368] Human antibodies can also be produced using transgenic mice which are incapable of expressing functional endogenous immunoglobulins, but which can express human immunoglobulin genes. For example, the human heavy and light chain immunoglobulin gene complexes may be introduced randomly or by homologous recombination into mouse embryonic stem cells. Alternatively, the human variable region, constant region, and diversity region may be introduced into mouse embryonic stem cells in addition to the human heavy and light chain genes. The mouse heavy and light chain immunoglobulin genes may be rendered non-functional separately or simultaneously with the introduction of human immunoglobulin loci by homologous recombination. In particular, homozygous deletion of the JH region prevents endogenous antibody production. The modified embryonic stem cells

are expanded and microinjected into blastocysts to produce chimeric mice. The chimeric mice are then bred to produce homozygous offspring which express human antibodies. The transgenic mice are immunized in the normal fashion with a selected antigen, e.g., all or a portion of a polypeptide of the invention. Monoclonal antibodies directed against the antigen can be obtained from the immunized, transgenic mice using conventional hybridoma technology. The human immunoglobulin transgenes harbored by the transgenic mice rearrange during B cell differentiation, and subsequently undergo class switching and somatic mutation. Thus, using such a technique, it is possible to produce therapeutically useful IgG, IgA, IgM and IgE antibodies. For an overview of this technology for producing human antibodies, see Lonberg and Huszar, Int. Rev. Immunol. 13:65-93 (1995). For a detailed discussion of this technology for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, see, e.g., PCT publications WO 98/24893; WO 92/01047; WO 96/34096; WO 96/33735; European Patent No. 0 598 877; U.S. Patent Nos. 5,413,923; 5,625,126; 5,633,425; 5,569,825; 5,661,016; 5,545,806; 5,814,318; 5,885,793; 5,916,771; and 5,939,598, which are incorporated by reference herein in their entirety. In addition, companies such as Abgenix, Inc. (Freemont, CA) and Genpharm (San Jose, CA) can be engaged to provide human antibodies directed against a selected antigen using technology similar to that described above.

[369] Completely human antibodies which recognize a selected epitope can be generated using a technique referred to as "guided selection." In this approach a selected non-human monoclonal antibody, e.g., a mouse antibody, is used to guide the selection of a completely human antibody recognizing the same epitope. (Jespers et al., Bio/technology 12:899-903 (1988)).

[370] Further, antibodies to the polypeptides of the invention can, in turn, be utilized to generate anti-idiotype antibodies that “mimic” polypeptides of the invention using techniques well known to those skilled in the art. (See, e.g., Greenspan & Bona, FASEB J. 7(5):437-444; (1989) and Nissinoff, J. Immunol. 147(8):2429-2438 (1991)). For example, antibodies which bind to and competitively inhibit polypeptide multimerization and/or binding of a polypeptide of the invention to a ligand can be used to generate anti-idiotypes that “mimic” the polypeptide multimerization and/or binding domain and, as a consequence, bind to and neutralize polypeptide and/or its ligand. Such neutralizing anti-idiotypes or Fab fragments of such anti-idiotypes can be used in therapeutic regimens to neutralize polypeptide ligand. For

example, such anti-idiotypic antibodies can be used to bind a polypeptide of the invention and/or to bind its ligands/receptors, and thereby block its biological activity.

Polynucleotides Encoding Antibodies

[371] The invention further provides polynucleotides comprising a nucleotide sequence encoding an antibody of the invention and fragments thereof. The invention also encompasses polynucleotides that hybridize under stringent or alternatively, under lower stringency hybridization conditions, e.g., as defined supra, to polynucleotides that encode an antibody, preferably, that specifically binds to a polypeptide of the invention, preferably, an antibody that binds to a polypeptide having the amino acid sequence of SEQ ID NO:Y.

[372] The polynucleotides may be obtained, and the nucleotide sequence of the polynucleotides determined, by any method known in the art. For example, if the nucleotide sequence of the antibody is known, a polynucleotide encoding the antibody may be assembled from chemically synthesized oligonucleotides (e.g., as described in Kutmeier et al., BioTechniques 17:242 (1994)), which, briefly, involves the synthesis of overlapping oligonucleotides containing portions of the sequence encoding the antibody, annealing and ligating of those oligonucleotides, and then amplification of the ligated oligonucleotides by PCR.

[373] Alternatively, a polynucleotide encoding an antibody may be generated from nucleic acid from a suitable source. If a clone containing a nucleic acid encoding a particular antibody is not available, but the sequence of the antibody molecule is known, a nucleic acid encoding the immunoglobulin may be chemically synthesized or obtained from a suitable source (e.g., an antibody cDNA library, or a cDNA library generated from, or nucleic acid, preferably poly A+ RNA, isolated from, any tissue or cells expressing the antibody, such as hybridoma cells selected to express an antibody of the invention) by PCR amplification using synthetic primers hybridizable to the 3' and 5' ends of the sequence or by cloning using an oligonucleotide probe specific for the particular gene sequence to identify, e.g., a cDNA clone from a cDNA library that encodes the antibody. Amplified nucleic acids generated by PCR may then be cloned into replicable cloning vectors using any method well known in the art.

[374] Once the nucleotide sequence and corresponding amino acid sequence of the antibody is determined, the nucleotide sequence of the antibody may be manipulated using

methods well known in the art for the manipulation of nucleotide sequences, e.g., recombinant DNA techniques, site directed mutagenesis, PCR, etc. (see, for example, the techniques described in Sambrook et al., 1990, Molecular Cloning, A Laboratory Manual, 2d Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, NY and Ausubel et al., eds., 1998, Current Protocols in Molecular Biology, John Wiley & Sons, NY, which are both incorporated by reference herein in their entireties), to generate antibodies having a different amino acid sequence, for example to create amino acid substitutions, deletions, and/or insertions.

[375] In a specific embodiment, the amino acid sequence of the heavy and/or light chain variable domains may be inspected to identify the sequences of the complementarity determining regions (CDRs) by methods that are well know in the art, e.g., by comparison to known amino acid sequences of other heavy and light chain variable regions to determine the regions of sequence hypervariability. Using routine recombinant DNA techniques, one or more of the CDRs may be inserted within framework regions, e.g., into human framework regions to humanize a non-human antibody, as described supra. The framework regions may be naturally occurring or consensus framework regions, and preferably human framework regions (see, e.g., Chothia et al., J. Mol. Biol. 278: 457-479 (1998) for a listing of human framework regions). Preferably, the polynucleotide generated by the combination of the framework regions and CDRs encodes an antibody that specifically binds a polypeptide of the invention. Preferably, as discussed supra, one or more amino acid substitutions may be made within the framework regions, and, preferably, the amino acid substitutions improve binding of the antibody to its antigen. Additionally, such methods may be used to make amino acid substitutions or deletions of one or more variable region cysteine residues participating in an intrachain disulfide bond to generate antibody molecules lacking one or more intrachain disulfide bonds. Other alterations to the polynucleotide are encompassed by the present invention and within the skill of the art.

[376] In addition, techniques developed for the production of "chimeric antibodies" (Morrison et al., Proc. Natl. Acad. Sci. 81:851-855 (1984); Neuberger et al., Nature 312:604-608 (1984); Takeda et al., Nature 314:452-454 (1985)) by splicing genes from a mouse antibody molecule of appropriate antigen specificity together with genes from a human antibody molecule of appropriate biological activity can be used. As described supra, a chimeric antibody is a molecule in which different portions are derived from different

animal species, such as those having a variable region derived from a murine mAb and a human immunoglobulin constant region, e.g., humanized antibodies.

[377] Alternatively, techniques described for the production of single chain antibodies (U.S. Patent No. 4,946,778; Bird, Science 242:423- 42 (1988); Huston et al., Proc. Natl. Acad. Sci. USA 85:5879-5883 (1988); and Ward et al., Nature 334:544-54 (1989)) can be adapted to produce single chain antibodies. Single chain antibodies are formed by linking the heavy and light chain fragments of the Fv region via an amino acid bridge, resulting in a single chain polypeptide. Techniques for the assembly of functional Fv fragments in E. coli may also be used (Skerra et al., Science 242:1038- 1041 (1988)).

Methods of Producing Antibodies

[378] The antibodies of the invention can be produced by any method known in the art for the synthesis of antibodies, in particular, by chemical synthesis or preferably, by recombinant expression techniques.

[379] Recombinant expression of an antibody of the invention, or fragment, derivative or analog thereof, (e.g., a heavy or light chain of an antibody of the invention or a single chain antibody of the invention), requires construction of an expression vector containing a polynucleotide that encodes the antibody. Once a polynucleotide encoding an antibody molecule or a heavy or light chain of an antibody, or portion thereof (preferably containing the heavy or light chain variable domain), of the invention has been obtained, the vector for the production of the antibody molecule may be produced by recombinant DNA technology using techniques well known in the art. Thus, methods for preparing a protein by expressing a polynucleotide containing an antibody encoding nucleotide sequence are described herein. Methods which are well known to those skilled in the art can be used to construct expression vectors containing antibody coding sequences and appropriate transcriptional and translational control signals. These methods include, for example, in vitro recombinant DNA techniques, synthetic techniques, and in vivo genetic recombination. The invention, thus, provides replicable vectors comprising a nucleotide sequence encoding an antibody molecule of the invention, or a heavy or light chain thereof, or a heavy or light chain variable domain, operably linked to a promoter. Such vectors may include the nucleotide sequence encoding the constant region of the antibody molecule (see, e.g., PCT Publication WO 86/05807; PCT

Publication WO 89/01036; and U.S. Patent No. 5,122,464) and the variable domain of the antibody may be cloned into such a vector for expression of the entire heavy or light chain.

[380] The expression vector is transferred to a host cell by conventional techniques and the transfected cells are then cultured by conventional techniques to produce an antibody of the invention. Thus, the invention includes host cells containing a polynucleotide encoding an antibody of the invention, or a heavy or light chain thereof, or a single chain antibody of the invention, operably linked to a heterologous promoter. In preferred embodiments for the expression of double-chained antibodies, vectors encoding both the heavy and light chains may be co-expressed in the host cell for expression of the entire immunoglobulin molecule, as detailed below.

[381] A variety of host-expression vector systems may be utilized to express the antibody molecules of the invention. Such host-expression systems represent vehicles by which the coding sequences of interest may be produced and subsequently purified, but also represent cells which may, when transformed or transfected with the appropriate nucleotide coding sequences, express an antibody molecule of the invention in situ. These include but are not limited to microorganisms such as bacteria (e.g., E. coli, B. subtilis) transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing antibody coding sequences; yeast (e.g., Saccharomyces, Pichia) transformed with recombinant yeast expression vectors containing antibody coding sequences; insect cell systems infected with recombinant virus expression vectors (e.g., baculovirus) containing antibody coding sequences; plant cell systems infected with recombinant virus expression vectors (e.g., cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant plasmid expression vectors (e.g., Ti plasmid) containing antibody coding sequences; or mammalian cell systems (e.g., COS, CHO, BHK, 293, 3T3 cells) harboring recombinant expression constructs containing promoters derived from the genome of mammalian cells (e.g., metallothionein promoter) or from mammalian viruses (e.g., the adenovirus late promoter; the vaccinia virus 7.5K promoter). Preferably, bacterial cells such as Escherichia coli, and more preferably, eukaryotic cells, especially for the expression of whole recombinant antibody molecule, are used for the expression of a recombinant antibody molecule. For example, mammalian cells such as Chinese hamster ovary cells (CHO), in conjunction with a vector such as the major intermediate early gene promoter element from

human cytomegalovirus is an effective expression system for antibodies (Foecking et al., Gene 45:101 (1986); Cockett et al., Bio/Technology 8:2 (1990)).

[382] In bacterial systems, a number of expression vectors may be advantageously selected depending upon the use intended for the antibody molecule being expressed. For example, when a large quantity of such a protein is to be produced, for the generation of pharmaceutical compositions of an antibody molecule, vectors which direct the expression of high levels of fusion protein products that are readily purified may be desirable. Such vectors include, but are not limited, to the E. coli expression vector pUR278 (Ruther et al., EMBO J. 2:1791 (1983)), in which the antibody coding sequence may be ligated individually into the vector in frame with the lac Z coding region so that a fusion protein is produced; pIN vectors (Inouye & Inouye, Nucleic Acids Res. 13:3101-3109 (1985); Van Heeke & Schuster, J. Biol. Chem. 24:5503-5509 (1989)); and the like. pGEX vectors may also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption and binding to matrix glutathione-agarose beads followed by elution in the presence of free glutathione. The pGEX vectors are designed to include thrombin or factor Xa protease cleavage sites so that the cloned target gene product can be released from the GST moiety.

[383] In an insect system, Autographa californica nuclear polyhedrosis virus (AcNPV) is used as a vector to express foreign genes. The virus grows in *Spodoptera frugiperda* cells. The antibody coding sequence may be cloned individually into non-essential regions (for example the polyhedrin gene) of the virus and placed under control of an AcNPV promoter (for example the polyhedrin promoter).

[384] In mammalian host cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, the antibody coding sequence of interest may be ligated to an adenovirus transcription/translation control complex, e.g., the late promoter and tripartite leader sequence. This chimeric gene may then be inserted in the adenovirus genome by in vitro or in vivo recombination. Insertion in a non-essential region of the viral genome (e.g., region E1 or E3) will result in a recombinant virus that is viable and capable of expressing the antibody molecule in infected hosts. (e.g., see Logan & Shenk, Proc. Natl. Acad. Sci. USA 81:355-359 (1984)). Specific initiation signals may also be required for efficient translation of inserted antibody coding sequences. These signals include the ATG initiation codon and adjacent sequences. Furthermore, the initiation

codon must be in phase with the reading frame of the desired coding sequence to ensure translation of the entire insert. These exogenous translational control signals and initiation codons can be of a variety of origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of appropriate transcription enhancer elements, transcription terminators, etc. (see Bittner et al., Methods in Enzymol. 153:51-544 (1987)).

[385] In addition, a host cell strain may be chosen which modulates the expression of the inserted sequences, or modifies and processes the gene product in the specific fashion desired. Such modifications (e.g., glycosylation) and processing (e.g., cleavage) of protein products may be important for the function of the protein. Different host cells have characteristic and specific mechanisms for the post-translational processing and modification of proteins and gene products. Appropriate cell lines or host systems can be chosen to ensure the correct modification and processing of the foreign protein expressed. To this end, eukaryotic host cells which possess the cellular machinery for proper processing of the primary transcript, glycosylation, and phosphorylation of the gene product may be used. Such mammalian host cells include but are not limited to CHO, VERY, BHK, Hela, COS, MDCK, 293, 3T3, WI38, and in particular, breast cancer cell lines such as, for example, BT483, Hs578T, HTB2, BT20 and T47D, and normal mammary gland cell line such as, for example, CRL7030 and Hs578Bst.

[386] For long-term, high-yield production of recombinant proteins, stable expression is preferred. For example, cell lines which stably express the antibody molecule may be engineered. Rather than using expression vectors which contain viral origins of replication, host cells can be transformed with DNA controlled by appropriate expression control elements (e.g., promoter, enhancer, sequences, transcription terminators, polyadenylation sites, etc.), and a selectable marker. Following the introduction of the foreign DNA

[387] A number of selection systems may be used, including but not limited to the herpes simplex virus thymidine kinase (Wigler et al., Cell 11:223 (1977)), hypoxanthine-guanine phosphoribosyltransferase (Szybalska & Szybalski, Proc. Natl. Acad. Sci. USA 48:202 (1992)), and adenine phosphoribosyltransferase (Lowy et al., Cell 22:817 (1980)) genes can be employed in tk-, hgprt- or aprt- cells, respectively. Also, antimetabolite resistance can be used as the basis of selection for the following genes: dhfr, which confers resistance to methotrexate (Wigler et al., Natl. Acad. Sci. USA 77:357 (1980); O'Hare et al., Proc. Natl. Acad. Sci. USA 78:1527 (1981)); gpt, which confers resistance to mycophenolic acid (Mulligan & Berg, Proc. Natl. Acad. Sci. USA 78:2072 (1981)); neo, which confers resistance to the aminoglycoside G-418 Clinical Pharmacy 12:488-505; Wu and Wu, Biotherapy 3:87-95 (1991); Tolstoshev, Ann. Rev. Pharmacol. Toxicol. 32:573-596 (1993); Mulligan, Science 260:926-932 (1993); and Morgan and Anderson, Ann. Rev. Biochem. 62:191-217 (1993); May, 1993, TIB TECH 11(5):155-215); and hygro, which confers resistance to hygromycin (Santerre et al., Gene 30:147 (1984)). Methods commonly known in the art of recombinant DNA technology may be routinely applied to select the desired recombinant clone, and such methods are described, for example, in Ausubel et al. (eds.), Current Protocols in Molecular Biology, John Wiley & Sons, NY (1993); Kriegler, Gene Transfer and Expression, A Laboratory Manual, Stockton Press, NY (1990); and in Chapters 12 and 13, Dracopoli et al. (eds), Current Protocols in Human Genetics, John Wiley & Sons, NY (1994); Colberre-Garapin et al., J. Mol. Biol. 150:1 (1981), which are incorporated by reference herein in their entireties.

[388] The expression levels of an antibody molecule can be increased by vector amplification (for a review, see Bebbington and Hentschel, The use of vectors based on gene amplification for the expression of cloned genes in mammalian cells in DNA cloning, Vol.3. (Academic Press, New York, 1987)). When a marker in the vector system expressing antibody is amplifiable, increase in the level of inhibitor present in culture of host cell will increase the number of copies of the marker gene. Since the amplified region is associated with the antibody gene, production of the antibody will also increase (Crouse et al., Mol. Cell. Biol. 3:257 (1983)).

[389] The host cell may be co-transfected with two expression vectors of the invention, the first vector encoding a heavy chain derived polypeptide and the second vector encoding a light chain derived polypeptide. The two vectors may contain identical selectable markers

which enable equal expression of heavy and light chain polypeptides. Alternatively, a single vector may be used which encodes, and is capable of expressing, both heavy and light chain polypeptides. In such situations, the light chain should be placed before the heavy chain to avoid an excess of toxic free heavy chain (Proudfoot, Nature 322:52 (1986); Kohler, Proc. Natl. Acad. Sci. USA 77:2197 (1980)). The coding sequences for the heavy and light chains may comprise cDNA or genomic DNA.

[390] Once an antibody molecule of the invention has been produced by an animal, chemically synthesized, or recombinantly expressed, it may be purified by any method known in the art for purification of an immunoglobulin molecule, for example, by chromatography (e.g., ion exchange, affinity, particularly by affinity for the specific antigen after Protein A, and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of proteins. In addition, the antibodies of the present invention or fragments thereof can be fused to heterologous polypeptide sequences described herein or otherwise known in the art, to facilitate purification.

[391] The present invention encompasses antibodies recombinantly fused or chemically conjugated (including both covalently and non-covalently conjugations) to a polypeptide (or portion thereof, preferably at least 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 amino acids of the polypeptide) of the present invention to generate fusion proteins. The fusion does not necessarily need to be direct, but may occur through linker sequences. The antibodies may be specific for antigens other than polypeptides (or portion thereof, preferably at least 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 amino acids of the polypeptide) of the present invention. For example, antibodies may be used to target the polypeptides of the present invention to particular cell types, either in vitro or in vivo, by fusing or conjugating the polypeptides of the present invention to antibodies specific for particular cell surface receptors. Antibodies fused or conjugated to the polypeptides of the present invention may also be used in in vitro immunoassays and purification methods using methods known in the art. See e.g., Harbor et al., supra, and PCT publication WO 93/21232; EP 439,095; Naramura et al., Immunol. Lett. 39:91-99 (1994); U.S. Patent 5,474,981; Gillies et al., PNAS 89:1428-1432 (1992); Fell et al., J. Immunol. 146:2446-2452(1991), which are incorporated by reference in their entireties.

[392] The present invention further includes compositions comprising the polypeptides of the present invention fused or conjugated to antibody domains other than the variable regions. For example, the polypeptides of the present invention may be fused or conjugated

to an antibody Fc region, or portion thereof. The antibody portion fused to a polypeptide of the present invention may comprise the constant region, hinge region, CH1 domain, CH2 domain, and CH3 domain or any combination of whole domains or portions thereof. The polypeptides may also be fused or conjugated to the above antibody portions to form multimers. For example, Fc portions fused to the polypeptides of the present invention can form dimers through disulfide bonding between the Fc portions. Higher multimeric forms can be made by fusing the polypeptides to portions of IgA and IgM. Methods for fusing or conjugating the polypeptides of the present invention to antibody portions are known in the art. See, e.g., U.S. Patent Nos. 5,336,603; 5,622,929; 5,359,046; 5,349,053; 5,447,851; 5,112,946; EP 307,434; EP 367,166; PCT publications WO 96/04388; WO 91/06570; Ashkenazi et al., Proc. Natl. Acad. Sci. USA 88:10535-10539 (1991); Zheng et al., J. Immunol. 154:5590-5600 (1995); and Vil et al., Proc. Natl. Acad. Sci. USA 89:11337-11341(1992) (said references incorporated by reference in their entireties).

[393] As discussed, supra, the polypeptides corresponding to a polypeptide, polypeptide fragment, or a variant of SEQ ID NO:Y may be fused or conjugated to the above antibody portions to increase the in vivo half life of the polypeptides or for use in immunoassays using methods known in the art. Further, the polypeptides corresponding to SEQ ID NO:Y may be fused or conjugated to the above antibody portions to facilitate purification. One reported example describes chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. (EP 394,827; Traunecker et al., Nature 331:84-86 (1988). The polypeptides of the present invention fused or conjugated to an antibody having disulfide- linked dimeric structures (due to the IgG) may also be more efficient in binding and neutralizing other molecules, than the monomeric secreted protein or protein fragment alone. (Fountoulakis et al., J. Biochem. 270:3958-3964 (1995)). In many cases, the Fc part in a fusion protein is beneficial in therapy and diagnosis, and thus can result in, for example, improved pharmacokinetic properties. (EP A 232,262). Alternatively, deleting the Fc part after the fusion protein has been expressed, detected, and purified, would be desired. For example, the Fc portion may hinder therapy and diagnosis if the fusion protein is used as an antigen for immunizations. In drug discovery, for example, human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to

identify antagonists of hIL-5. (See, Bennett et al., J. Molecular Recognition 8:52-58 (1995); Johanson et al., J. Biol. Chem. 270:9459-9471 (1995).

[394] Moreover, the antibodies or fragments thereof of the present invention can be fused to marker sequences, such as a peptide to facilitate purification. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et al., Proc. Natl. Acad. Sci. USA 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Other peptide tags useful for purification include, but are not limited to, the "HA" tag, which corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson et al., Cell 37:767 (1984)) and the "flag" tag.

[395] The present invention further encompasses antibodies or fragments thereof conjugated to a diagnostic or therapeutic agent. The antibodies can be used diagnostically to, for example, monitor the development or progression of a tumor as part of a clinical testing procedure to, e.g., determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, radioactive materials, positron emitting metals using various positron emission tomographies, and nonradioactive paramagnetic metal ions. The detectable substance may be coupled or conjugated either directly to the antibody (or fragment thereof) or indirectly, through an intermediate (such as, for example, a linker known in the art) using techniques known in the art. See, for example, U.S. Patent No. 4,741,900 for metal ions which can be conjugated to antibodies for use as diagnostics according to the present invention. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin; and examples of suitable radioactive material include 125I, 131I, 111In or 99Tc.

[396] Further, an antibody or fragment thereof may be conjugated to a therapeutic moiety such as a cytotoxin, e.g., a cytostatic or cytocidal agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example, 213Bi. A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include paclitaxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (e.g., mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclothosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis- dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (e.g., daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (e.g., dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (e.g., vincristine and vinblastine).

[397] The conjugates of the invention can be used for modifying a given biological response, the therapeutic agent or drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a protein such as tumor necrosis factor, a-interferon, ß-interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator, an apoptotic agent, e.g., TNF-alpha, TNF-beta, AIM I (See, International Publication No. WO 97/33899), AIM II (See, International Publication No. WO 97/34911), Fas Ligand (Takahashi *et al., Int. Immunol., 6*:1567-1574 (1994)), VEGI (See, International Publication No. WO 99/23105), a thrombotic agent or an anti- angiogenic agent, e.g., angiostatin or endostatin; or, biological response modifiers such as, for example, lymphokines, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophage colony stimulating factor ("GM-CSF"), granulocyte colony stimulating factor ("G-CSF"), or other growth factors.

[398] Antibodies may also be attached to solid supports, which are particularly useful for immunoassays or purification of the target antigen. Such solid supports include, but are not

limited to, glass, cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene.

[399] Techniques for conjugating such therapeutic moiety to antibodies are well known, see, e.g., Arnon et al., "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in Monoclonal Antibodies And Cancer Therapy, Reisfeld et al. (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom et al., "Antibodies For Drug Delivery", in Controlled Drug Delivery (2nd Ed.), Robinson et al. (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in Monoclonal Antibodies '84: Biological And Clinical Applications, Pinchera et al. (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in Monoclonal Antibodies For Cancer Detection And Therapy, Baldwin et al. (eds.), pp. 303-16 (Academic Press 1985), and Thorpe et al., "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", Immunol. Rev. 62:119-58 (1982).

[400] Alternatively, an antibody can be conjugated to a second antibody to form an antibody heteroconjugate as described by Segal in U.S. Patent No. 4,676,980, which is incorporated herein by reference in its entirety.

[401] An antibody, with or without a therapeutic moiety conjugated to it, administered alone or in combination with cytotoxic factor(s) and/or cytokine(s) can be used as a therapeutic.

Immunophenotyping

[402] The antibodies of the invention may be utilized for immunophenotyping of cell lines and biological samples. The translation product of the gene of the present invention may be useful as a cell specific marker, or more specifically as a cellular marker that is differentially expressed at various stages of differentiation and/or maturation of particular cell types. Monoclonal antibodies directed against a specific epitope, or combination of epitopes, will allow for the screening of cellular populations expressing the marker. Various techniques can be utilized using monoclonal antibodies to screen for cellular populations expressing the marker(s), and include magnetic separation using antibody-coated magnetic beads, "panning" with antibody attached to a solid matrix (i.e., plate), and flow cytometry (See, e.g., U.S. Patent 5,985,660; and Morrison *et al., Cell, 96*:737-49 (1999)).

[403] These techniques allow for the screening of particular populations of cells, such as might be found with hematological malignancies (i.e. minimal residual disease (MRD) in acute leukemic patients) and "non-self" cells in transplantations to prevent Graft-versus-Host Disease (GVHD). Alternatively, these techniques allow for the screening of hematopoietic stem and progenitor cells capable of undergoing proliferation and/or differentiation, as might be found in human umbilical cord blood.

Assays For Antibody Binding

[404] The antibodies of the invention may be assayed for immunospecific binding by any method known in the art. The immunoassays which can be used include but are not limited to competitive and non-competitive assay systems using techniques such as western blots, radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoprecipitation assays, precipitin reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, protein A immunoassays, to name but a few. Such assays are routine and well known in the art (see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York, which is incorporated by reference herein in its entirety). Exemplary immunoassays are described briefly below (but are not intended by way of limitation).

[405] Immunoprecipitation protocols generally comprise lysing a population of cells in a lysis buffer such as RIPA buffer (1% NP-40 or Triton X- 100, 1% sodium deoxycholate, 0.1% SDS, 0.15 M NaCl, 0.01 M sodium phosphate at pH 7.2, 1% Trasylol) supplemented with protein phosphatase and/or protease inhibitors (e.g., EDTA, PMSF, aprotinin, sodium vanadate), adding the antibody of interest to the cell lysate, incubating for a period of time (e.g., 1-4 hours) at 4° C, adding protein A and/or protein G sepharose beads to the cell lysate, incubating for about an hour or more at 4° C, washing the beads in lysis buffer and resuspending the beads in SDS/sample buffer. The ability of the antibody of interest to immunoprecipitate a particular antigen can be assessed by, e.g., western blot analysis. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the binding of the antibody to an antigen and decrease the background (e.g., pre-clearing the cell lysate with sepharose beads). For further discussion regarding immunoprecipitation

protocols see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 10.16.1.

[406] Western blot analysis generally comprises preparing protein samples, electrophoresis of the protein samples in a polyacrylamide gel (e.g., 8%- 20% SDS-PAGE depending on the molecular weight of the antigen), transferring the protein sample from the polyacrylamide gel to a membrane such as nitrocellulose, PVDF or nylon, blocking the membrane in blocking solution (e.g., PBS with 3% BSA or non-fat milk), washing the membrane in washing buffer (e.g., PBS-Tween 20), blocking the membrane with primary antibody (the antibody of interest) diluted in blocking buffer, washing the membrane in washing buffer, blocking the membrane with a secondary antibody (which recognizes the primary antibody, e.g., an anti-human antibody) conjugated to an enzymatic substrate (e.g., horseradish peroxidase or alkaline phosphatase) or radioactive molecule (e.g., 32P or 125I) diluted in blocking buffer, washing the membrane in wash buffer, and detecting the presence of the antigen. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected and to reduce the background noise. For further discussion regarding western blot protocols see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 10.8.1.

[407] ELISAs comprise preparing antigen, coating the well of a 96 well microtiter plate with the antigen, adding the antibody of interest conjugated to a detectable compound such as an enzymatic substrate (e.g., horseradish peroxidase or alkaline phosphatase) to the well and incubating for a period of time, and detecting the presence of the antigen. In ELISAs the antibody of interest does not have to be conjugated to a detectable compound; instead, a second antibody (which recognizes the antibody of interest) conjugated to a detectable compound may be added to the well. Further, instead of coating the well with the antigen, the antibody may be coated to the well. In this case, a second antibody conjugated to a detectable compound may be added following the addition of the antigen of interest to the coated well. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected as well as other variations of ELISAs known in the art. For further discussion regarding ELISAs see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 11.2.1.

[408] The binding affinity of an antibody to an antigen and the off-rate of an antibody-antigen interaction can be determined by competitive binding assays. One example of a

competitive binding assay is a radioimmunoassay comprising the incubation of labeled antigen (e.g., 3H or 125I) with the antibody of interest in the presence of increasing amounts of unlabeled antigen, and the detection of the antibody bound to the labeled antigen. The affinity of the antibody of interest for a particular antigen and the binding off-rates can be determined from the data by scatchard plot analysis. Competition with a second antibody can also be determined using radioimmunoassays. In this case, the antigen is incubated with antibody of interest conjugated to a labeled compound (e.g., 3H or 125I) in the presence of increasing amounts of an unlabeled second antibody.

Therapeutic Uses

[409] The present invention is further directed to antibody-based therapies which involve administering antibodies of the invention to an animal, preferably a mammal, and most preferably a human, patient for treating one or more of the disclosed diseases, disorders, or conditions. Therapeutic compounds of the invention include, but are not limited to, antibodies of the invention (including fragments, analogs and derivatives thereof as described herein) and nucleic acids encoding antibodies of the invention (including fragments, analogs and derivatives thereof and anti-idiotypic antibodies as described herein). The antibodies of the invention can be used to treat, inhibit or prevent diseases, disorders or conditions associated with aberrant expression and/or activity of a polypeptide of the invention, including, but not limited to, any one or more of the diseases, disorders, or conditions described herein. The treatment and/or prevention of diseases, disorders, or conditions associated with aberrant expression and/or activity of a polypeptide of the invention includes, but is not limited to, alleviating symptoms associated with those diseases, disorders or conditions. Antibodies of the invention may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

[410] A summary of the ways in which the antibodies of the present invention may be used therapeutically includes binding polynucleotides or polypeptides of the present invention locally or systemically in the body or by direct cytotoxicity of the antibody, e.g. as mediated by complement (CDC) or by effector cells (ADCC). Some of these approaches are described in more detail below. Armed with the teachings provided herein, one of ordinary skill in the art will know how to use the antibodies of the present invention for diagnostic, monitoring or therapeutic purposes without undue experimentation.

[411] The antibodies of this invention may be advantageously utilized in combination with other monoclonal or chimeric antibodies, or with lymphokines or hematopoietic growth factors (such as, e.g., IL-2, IL-3 and IL-7), for example, which serve to increase the number or activity of effector cells which interact with the antibodies.

[412] The antibodies of the invention may be administered alone or in combination with other types of treatments (e.g., radiation therapy, chemotherapy, hormonal therapy, immunotherapy and anti-tumor agents). Generally, administration of products of a species origin or species reactivity (in the case of antibodies) that is the same species as that of the patient is preferred. Thus, in a preferred embodiment, human antibodies, fragments derivatives, analogs, or nucleic acids, are administered to a human patient for therapy or prophylaxis.

[413] It is preferred to use high affinity and/or potent in vivo inhibiting and/or neutralizing antibodies against polypeptides or polynucleotides of the present invention, fragments or regions thereof, for both immunoassays directed to and therapy of disorders related to polynucleotides or polypeptides, including fragments thereof, of the present invention. Such antibodies, fragments, or regions, will preferably have an affinity for polynucleotides or polypeptides of the invention, including fragments thereof. Preferred binding affinities include those with a dissociation constant or Kd less than 5×10^{-2} M, 10^{-2} M, 5×10^{-3} M, 10^{-3} M, 5×10^{-4} M, 10^{-4} M, 5×10^{-5} M, 10^{-5} M, 5×10^{-6} M, 10^{-6} M, 5×10^{-7} M, 10^{-7} M, 5×10^{-8} M, 10^{-8} M, 5×10^{-9} M, 10^{-9} M, 5×10^{-10} M, 10^{-10} M, 5×10^{-11} M, 10^{-11} M, 5×10^{-12} M, 10^{-12} M, 5×10^{-13} M, 10^{-13} M, 5×10^{-14} M, 10^{-14} M, 5×10^{-15} M, and 10^{-15} M.

Gene Therapy

[414] In a specific embodiment, nucleic acids comprising sequences encoding antibodies or functional derivatives thereof, are administered to treat, inhibit or prevent a disease or disorder associated with aberrant expression and/or activity of a polypeptide of the invention, by way of gene therapy. Gene therapy refers to therapy performed by the administration to a subject of an expressed or expressible nucleic acid. In this embodiment of the invention, the nucleic acids produce their encoded protein that mediates a therapeutic effect.

[415] Any of the methods for gene therapy available in the art can be used according to the present invention. Exemplary methods are described below.

[416] For general reviews of the methods of gene therapy, see Goldspiel et al., Clinical Pharmacy 12:488-505 (1993); Wu and Wu, Biotherapy 3:87-95 (1991); Tolstoshev, Ann. Rev. Pharmacol. Toxicol. 32:573-596 (1993); Mulligan, Science 260:926-932 (1993); and Morgan and Anderson, Ann. Rev. Biochem. 62:191-217 (1993); May, TIBTECH 11(5):155-215 (1993). Methods commonly known in the art of recombinant DNA technology which can be used are described in Ausubel et al. (eds.), Current Protocols in Molecular Biology, John Wiley & Sons, NY (1993); and Kriegler, Gene Transfer and Expression, A Laboratory Manual, Stockton Press, NY (1990).

[417] In a preferred aspect, the compound comprises nucleic acid sequences encoding an antibody, said nucleic acid sequences being part of expression vectors that express the antibody or fragments or chimeric proteins or heavy or light chains thereof in a suitable host. In particular, such nucleic acid sequences have promoters operably linked to the antibody coding region, said promoter being inducible or constitutive, and, optionally, tissue-specific. In another particular embodiment, nucleic acid molecules are used in which the antibody coding sequences and any other desired sequences are flanked by regions that promote homologous recombination at a desired site in the genome, thus providing for intrachromosomal expression of the antibody encoding nucleic acids (Koller and Smithies, Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); Zijlstra et al., Nature 342:435-438 (1989). In specific embodiments, the expressed antibody molecule is a single chain antibody; alternatively, the nucleic acid sequences include sequences encoding both the heavy and light chains, or fragments thereof, of the antibody.

[418] Delivery of the nucleic acids into a patient may be either direct, in which case the patient is directly exposed to the nucleic acid or nucleic acid- carrying vectors, or indirect, in which case, cells are first transformed with the nucleic acids in vitro, then transplanted into the patient. These two approaches are known, respectively, as in vivo or ex vivo gene therapy.

[419] In a specific embodiment, the nucleic acid sequences are directly administered in vivo, where it is expressed to produce the encoded product. This can be accomplished by any of numerous methods known in the art, e.g., by constructing them as part of an appropriate nucleic acid expression vector and administering it so that they become intracellular, e.g., by infection using defective or attenuated retrovirals or other viral vectors (see U.S. Patent No. 4,980,286), or by direct injection of naked DNA, or by use of

microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, encapsulation in liposomes, microparticles, or microcapsules, or by administering them in linkage to a peptide which is known to enter the nucleus, by administering it in linkage to a ligand subject to receptor-mediated endocytosis (see, e.g., Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)) (which can be used to target cell types specifically expressing the receptors), etc. In another embodiment, nucleic acid-ligand complexes can be formed in which the ligand comprises a fusogenic viral peptide to disrupt endosomes, allowing the nucleic acid to avoid lysosomal degradation. In yet another embodiment, the nucleic acid can be targeted in vivo for cell specific uptake and expression, by targeting a specific receptor (see, e.g., PCT Publications WO 92/06180; WO 92/22635; WO92/20316; WO93/14188, WO 93/20221). Alternatively, the nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination (Koller and Smithies, Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); Zijlstra et al., Nature 342:435-438 (1989)).

[420] In a specific embodiment, viral vectors that contains nucleic acid sequences encoding an antibody of the invention are used. For example, a retroviral vector can be used (see Miller et al., Meth. Enzymol. 217:581-599 (1993)). These retroviral vectors contain the components necessary for the correct packaging of the viral genome and integration into the host cell DNA. The nucleic acid sequences encoding the antibody to be used in gene therapy are cloned into one or more vectors, which facilitates delivery of the gene into a patient. More detail about retroviral vectors can be found in Boesen et al., Biotherapy 6:291-302 (1994), which describes the use of a retroviral vector to deliver the mdr1 gene to hematopoietic stem cells in order to make the stem cells more resistant to chemotherapy. Other references illustrating the use of retroviral vectors in gene therapy are: Clowes et al., J. Clin. Invest. 93:644-651 (1994); Kiem et al., Blood 83:1467-1473 (1994); Salmons and Gunzberg, Human Gene Therapy 4:129-141 (1993); and Grossman and Wilson, Curr. Opin. in Genetics and Devel. 3:110-114 (1993).

[421] Adenoviruses are other viral vectors that can be used in gene therapy. Adenoviruses are especially attractive vehicles for delivering genes to respiratory epithelia. Adenoviruses naturally infect respiratory epithelia where they cause a mild disease. Other targets for adenovirus-based delivery systems are liver, the central nervous system, endothelial cells, and muscle. Adenoviruses have the advantage of being capable of infecting

non-dividing cells. Kozarsky and Wilson, Current Opinion in Genetics and Development 3:499-503 (1993) present a review of adenovirus-based gene therapy. Bout et al., Human Gene Therapy 5:3-10 (1994) demonstrated the use of adenovirus vectors to transfer genes to the respiratory epithelia of rhesus monkeys. Other instances of the use of adenoviruses in gene therapy can be found in Rosenfeld et al., Science 252:431-434 (1991); Rosenfeld et al., Cell 68:143- 155 (1992); Mastrangeli et al., J. Clin. Invest. 91:225-234 (1993); PCT Publication WO94/12649; and Wang, et al., Gene Therapy 2:775-783 (1995). In a preferred embodiment, adenovirus vectors are used.

[422] Adeno-associated virus (AAV) has also been proposed for use in gene therapy (Walsh et al., Proc. Soc. Exp. Biol. Med. 204:289-300 (1993); U.S. Patent No. 5,436,146).

[423] Another approach to gene therapy involves transferring a gene to cells in tissue culture by such methods as electroporation, lipofection, calcium phosphate mediated transfection, or viral infection. Usually, the method of transfer includes the transfer of a selectable marker to the cells. The cells are then placed under selection to isolate those cells that have taken up and are expressing the transferred gene. Those cells are then delivered to a patient.

[424] In this embodiment, the nucleic acid is introduced into a cell prior to administration in vivo of the resulting recombinant cell. Such introduction can be carried out by any method known in the art, including but not limited to transfection, electroporation, microinjection, infection with a viral or bacteriophage vector containing the nucleic acid sequences, cell fusion, chromosome-mediated gene transfer, microcell-mediated gene transfer, spheroplast fusion, etc. Numerous techniques are known in the art for the introduction of foreign genes into cells (see, e.g., Loeffler and Behr, Meth. Enzymol. 217:599-618 (1993); Cohen et al., Meth. Enzymol. 217:618-644 (1993); Cline, Pharmac. Ther. 29:69-92m (1985) and may be used in accordance with the present invention, provided that the necessary developmental and physiological functions of the recipient cells are not disrupted. The technique should provide for the stable transfer of the nucleic acid to the cell, so that the nucleic acid is expressible by the cell and preferably heritable and expressible by its cell progeny.

[425] The resulting recombinant cells can be delivered to a patient by various methods known in the art. Recombinant blood cells (e.g., hematopoietic stem or progenitor cells) are

preferably administered intravenously. The amount of cells envisioned for use depends on the desired effect, patient state, etc., and can be determined by one skilled in the art.

[426] Cells into which a nucleic acid can be introduced for purposes of gene therapy encompass any desired, available cell type, and include but are not limited to epithelial cells, endothelial cells, keratinocytes, fibroblasts, muscle cells, hepatocytes; blood cells such as T lymphocytes, B lymphocytes, monocytes, macrophages, neutrophils, eosinophils, megakaryocytes, granulocytes; various stem or progenitor cells, in particular hematopoietic stem or progenitor cells, e.g., as obtained from bone marrow, umbilical cord blood, peripheral blood, fetal liver, etc.

[427] In a preferred embodiment, the cell used for gene therapy is autologous to the patient.

[428] In an embodiment in which recombinant cells are used in gene therapy, nucleic acid sequences encoding an antibody are introduced into the cells such that they are expressible by the cells or their progeny, and the recombinant cells are then administered in vivo for therapeutic effect. In a specific embodiment, stem or progenitor cells are used. Any stem and/or progenitor cells which can be isolated and maintained in vitro can potentially be used in accordance with this embodiment of the present invention (see e.g. PCT Publication WO 94/08598; Stemple and Anderson, Cell 71:973-985 (1992); Rheinwald, Meth. Cell Bio. 21A:229 (1980); and Pittelkow and Scott, Mayo Clinic Proc. 61:771 (1986)).

[429] In a specific embodiment, the nucleic acid to be introduced for purposes of gene therapy comprises an inducible promoter operably linked to the coding region, such that expression of the nucleic acid is controllable by controlling the presence or absence of the appropriate inducer of transcription. Demonstration of Therapeutic or Prophylactic Activity

[430] The compounds or pharmaceutical compositions of the invention are preferably tested in vitro, and then in vivo for the desired therapeutic or prophylactic activity, prior to use in humans. For example, in vitro assays to demonstrate the therapeutic or prophylactic utility of a compound or pharmaceutical composition include, the effect of a compound on a cell line or a patient tissue sample. The effect of the compound or composition on the cell line and/or tissue sample can be determined utilizing techniques known to those of skill in the art including, but not limited to, rosette formation assays and cell lysis assays. In accordance with the invention, in vitro assays which can be used to determine whether administration of a specific compound is indicated, include in vitro cell culture assays in which a patient tissue

sample is grown in culture, and exposed to or otherwise administered a compound, and the effect of such compound upon the tissue sample is observed.

Therapeutic/Prophylactic Administration and Composition

[431] The invention provides methods of treatment, inhibition and prophylaxis by administration to a subject of an effective amount of a compound or pharmaceutical composition of the invention, preferably a polypeptide or antibody of the invention. In a preferred aspect, the compound is substantially purified (e.g., substantially free from substances that limit its effect or produce undesired side-effects). The subject is preferably an animal, including but not limited to animals such as cows, pigs, horses, chickens, cats, dogs, etc., and is preferably a mammal, and most preferably human.

[432] Formulations and methods of administration that can be employed when the compound comprises a nucleic acid or an immunoglobulin are described above; additional appropriate formulations and routes of administration can be selected from among those described herein below.

[433] Various delivery systems are known and can be used to administer a compound of the invention, e.g., encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the compound, receptor-mediated endocytosis (see, e.g., Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)), construction of a nucleic acid as part of a retroviral or other vector, etc. Methods of introduction include but are not limited to intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral routes. The compounds or compositions may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local. In addition, it may be desirable to introduce the pharmaceutical compounds or compositions of the invention into the central nervous system by any suitable route, including intraventricular and intrathecal injection; intraventricular injection may be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir. Pulmonary administration can also be employed, e.g., by use of an inhaler or nebulizer, and formulation with an aerosolizing agent.

[434] In a specific embodiment, it may be desirable to administer the pharmaceutical compounds or compositions of the invention locally to the area in need of treatment; this may be achieved by, for example, and not by way of limitation, local infusion during surgery, topical application, e.g., in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers. Preferably, when administering a protein, including an antibody, of the invention, care must be taken to use materials to which the protein does not absorb.

[435] In another embodiment, the compound or composition can be delivered in a vesicle, in particular a liposome (see Langer, Science 249:1527-1533 (1990); Treat et al., in Liposomes in the Therapy of Infectious Disease and Cancer, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 353- 365 (1989); Lopez-Berestein, ibid., pp. 317-327; see generally ibid.)

[436] In yet another embodiment, the compound or composition can be delivered in a controlled release system. In one embodiment, a pump may be used (see Langer, supra; Sefton, CRC Crit. Ref. Biomed. Eng. 14:201 (1987); Buchwald et al., Surgery 88:507 (1980); Saudek et al., N. Engl. J. Med. 321:574 (1989)). In another embodiment, polymeric materials can be used (see Medical Applications of Controlled Release, Langer and Wise (eds.), CRC Pres., Boca Raton, Florida (1974); Controlled Drug Bioavailability, Drug Product Design and Performance, Smolen and Ball (eds.), Wiley, New York (1984); Ranger and Peppas, J., Macromol. Sci. Rev. Macromol. Chem. 23:61 (1983); see also Levy et al., Science 228:190 (1985); During et al., Ann. Neurol. 25:351 (1989); Howard et al., J.Neurosurg. 71:105 (1989)). In yet another embodiment, a controlled release system can be placed in proximity of the therapeutic target, i.e., the brain, thus requiring only a fraction of the systemic dose (see, e.g., Goodson, in Medical Applications of Controlled Release, supra, vol. 2, pp. 115-138 (1984)).

[437] Other controlled release systems are discussed in the review by Langer (Science 249:1527-1533 (1990)).

[438] In a specific embodiment where the compound of the invention is a nucleic acid encoding a protein, the nucleic acid can be administered in vivo to promote expression of its encoded protein, by constructing it as part of an appropriate nucleic acid expression vector and administering it so that it becomes intracellular, e.g., by use of a retroviral vector (see

U.S. Patent No. 4,980,286), or by direct injection, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, or by administering it in linkage to a homeobox- like peptide which is known to enter the nucleus (see e.g., Joliot et al., Proc. Natl. Acad. Sci. USA 88:1864-1868 (1991)), etc. Alternatively, a nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination.

[439] The present invention also provides pharmaceutical compositions. Such compositions comprise a therapeutically effective amount of a compound, and a pharmaceutically acceptable carrier. In a specific embodiment, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin. Such compositions will contain a therapeutically effective amount of the compound, preferably in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration.

[440] In a preferred embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous administration to human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as lignocaine to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

[441] The compounds of the invention can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with anions such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with cations such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.

[442] The amount of the compound of the invention which will be effective in the treatment, inhibition and prevention of a disease or disorder associated with aberrant expression and/or activity of a polypeptide of the invention can be determined by standard clinical techniques. In addition, in vitro assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from in vitro or animal model test systems.

[443] For antibodies, the dosage administered to a patient is typically 0.1 mg/kg to 100 mg/kg of the patient's body weight. Preferably, the dosage administered to a patient is between 0.1 mg/kg and 20 mg/kg of the patient's body weight, more preferably 1 mg/kg to 10 mg/kg of the patient's body weight. Generally, human antibodies have a longer half-life within the human body than antibodies from other species due to the immune response to the foreign polypeptides. Thus, lower dosages of human antibodies and less frequent

administration is often possible. Further, the dosage and frequency of administration of antibodies of the invention may be reduced by enhancing uptake and tissue penetration (e.g., into the brain) of the antibodies by modifications such as, for example, lipidation.

[444] The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

Diagnosis and Imaging

[445] Labeled antibodies, and derivatives and analogs thereof, which specifically bind to a polypeptide of interest can be used for diagnostic purposes to detect, diagnose, or monitor diseases, disorders, and/or conditions associated with the aberrant expression and/or activity of a polypeptide of the invention. The invention provides for the detection of aberrant expression of a polypeptide of interest, comprising (a) assaying the expression of the polypeptide of interest in cells or body fluid of an individual using one or more antibodies specific to the polypeptide interest and (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is indicative of aberrant expression.

[446] The invention provides a diagnostic assay for diagnosing a disorder, comprising (a) assaying the expression of the polypeptide of interest in cells or body fluid of an individual using one or more antibodies specific to the polypeptide interest and (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is indicative of a particular disorder. With respect to cancer, the presence of a relatively high amount of transcript in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

[447] Antibodies of the invention can be used to assay protein levels in a biological sample using classical immunohistological methods known to those of skill in the art (e.g., see Jalkanen, et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, et al., J. Cell . Biol. 105:3087-3096 (1987)). Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase; radioisotopes, such as iodine (125I, 121I), carbon (14C), sulfur (35S), tritium (3H), indium (112In), and technetium (99Tc); luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

[448] One aspect of the invention is the detection and diagnosis of a disease or disorder associated with aberrant expression of a polypeptide of interest in an animal, preferably a mammal and most preferably a human. In one embodiment, diagnosis comprises: a) administering (for example, parenterally, subcutaneously, or intraperitoneally) to a subject an effective amount of a labeled molecule which specifically binds to the polypeptide of interest; b) waiting for a time interval following the administering for permitting the labeled molecule to preferentially concentrate at sites in the subject where the polypeptide is expressed (and for unbound labeled molecule to be cleared to background level); c) determining background level; and d) detecting the labeled molecule in the subject, such that detection of labeled molecule above the background level indicates that the subject has a particular disease or disorder associated with aberrant expression of the polypeptide of interest. Background level can be determined by various methods including, comparing the amount of labeled molecule detected to a standard value previously determined for a particular system.

[449] It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of 99mTc. The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which contain the specific protein. In vivo tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments." (Chapter 13

in Tumor Imaging: The Radiochemical Detection of Cancer, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982).

[450] Depending on several variables, including the type of label used and the mode of administration, the time interval following the administration for permitting the labeled molecule to preferentially concentrate at sites in the subject and for unbound labeled molecule to be cleared to background level is 6 to 48 hours or 6 to 24 hours or 6 to 12 hours. In another embodiment the time interval following administration is 5 to 20 days or 5 to 10 days.

[451] In an embodiment, monitoring of the disease or disorder is carried out by repeating the method for diagnosing the disease or disease, for example, one month after initial diagnosis, six months after initial diagnosis, one year after initial diagnosis, etc.

[452] Presence of the labeled molecule can be detected in the patient using methods known in the art for in vivo scanning. These methods depend upon the type of label used. Skilled artisans will be able to determine the appropriate method for detecting a particular label. Methods and devices that may be used in the diagnostic methods of the invention include, but are not limited to, computed tomography (CT), whole body scan such as position emission tomography (PET), magnetic resonance imaging (MRI), and sonography.

[453] In a specific embodiment, the molecule is labeled with a radioisotope and is detected in the patient using a radiation responsive surgical instrument (Thurston et al., U.S. Patent No. 5,441,050). In another embodiment, the molecule is labeled with a fluorescent compound and is detected in the patient using a fluorescence responsive scanning instrument. In another embodiment, the molecule is labeled with a positron emitting metal and is detected in the patent using positron emission-tomography. In yet another embodiment, the molecule is labeled with a paramagnetic label and is detected in a patient using magnetic resonance imaging (MRI).

Kits

[454] The present invention provides kits that can be used in the above methods. In one embodiment, a kit comprises an antibody of the invention, preferably a purified antibody, in one or more containers. In a specific embodiment, the kits of the present invention contain a substantially isolated polypeptide comprising an epitope which is specifically immunoreactive with an antibody included in the kit. Preferably, the kits of the present

invention further comprise a control antibody which does not react with the polypeptide of interest. In another specific embodiment, the kits of the present invention contain a means for detecting the binding of an antibody to a polypeptide of interest (e.g., the antibody may be conjugated to a detectable substrate such as a fluorescent compound, an enzymatic substrate, a radioactive compound or a luminescent compound, or a second antibody which recognizes the first antibody may be conjugated to a detectable substrate).

[455] In another specific embodiment of the present invention, the kit is a diagnostic kit for use in screening serum containing antibodies specific against proliferative and/or cancerous polynucleotides and polypeptides. Such a kit may include a control antibody that does not react with the polypeptide of interest. Such a kit may include a substantially isolated polypeptide antigen comprising an epitope which is specifically immunoreactive with at least one anti-polypeptide antigen antibody. Further, such a kit includes means for detecting the binding of said antibody to the antigen (e.g., the antibody may be conjugated to a fluorescent compound such as fluorescein or rhodamine which can be detected by flow cytometry). In specific embodiments, the kit may include a recombinantly produced or chemically synthesized polypeptide antigen. The polypeptide antigen of the kit may also be attached to a solid support.

[456] In a more specific embodiment the detecting means of the above-described kit includes a solid support to which said polypeptide antigen is attached. Such a kit may also include a non-attached reporter-labeled anti-human antibody. In this embodiment, binding of the antibody to the polypeptide antigen can be detected by binding of the said reporter-labeled antibody.

[457] In an additional embodiment, the invention includes a diagnostic kit for use in screening serum containing antigens of the polypeptide of the invention. The diagnostic kit includes a substantially isolated antibody specifically immunoreactive with polypeptide or polynucleotide antigens, and means for detecting the binding of the polynucleotide or polypeptide antigen to the antibody. In one embodiment, the antibody is attached to a solid support. In a specific embodiment, the antibody may be a monoclonal antibody. The detecting means of the kit may include a second, labeled monoclonal antibody. Alternatively, or in addition, the detecting means may include a labeled, competing antigen.

[458] In one diagnostic configuration, test serum is reacted with a solid phase reagent having a surface-bound antigen obtained by the methods of the present invention. After

binding with specific antigen antibody to the reagent and removing unbound serum components by washing, the reagent is reacted with reporter-labeled anti-human antibody to bind reporter to the reagent in proportion to the amount of bound anti-antigen antibody on the solid support. The reagent is again washed to remove unbound labeled antibody, and the amount of reporter associated with the reagent is determined. Typically, the reporter is an enzyme which is detected by incubating the solid phase in the presence of a suitable fluorometric, luminescent or colorimetric substrate (Sigma, St. Louis, MO).

[459] The solid surface reagent in the above assay is prepared by known techniques for attaching protein material to solid support material, such as polymeric beads, dip sticks, 96-well plate or filter material. These attachment methods generally include non-specific adsorption of the protein to the support or covalent attachment of the protein, typically through a free amine group, to a chemically reactive group on the solid support, such as an activated carboxyl, hydroxyl, or aldehyde group. Alternatively, streptavidin coated plates can be used in conjunction with biotinylated antigen(s).

[460] Thus, the invention provides an assay system or kit for carrying out this diagnostic method. The kit generally includes a support with surface- bound recombinant antigens, and a reporter-labeled anti-human antibody for detecting surface-bound anti-antigen antibody.

Uses of the Polynucleotides

[461] Each of the polynucleotides identified herein can be used in numerous ways as reagents. The following description should be considered exemplary and utilizes known techniques.

[462] The polynucleotides of the present invention are useful for chromosome identification. There exists an ongoing need to identify new chromosome markers, since few chromosome marking reagents, based on actual sequence data (repeat polymorphisms), are presently available. Each sequence is specifically targeted to and can hybridize with a particular location on an individual human chromosome, thus each polynucleotide of the present invention can routinely be used as a chromosome marker using techniques known in the art.

[463] Briefly, sequences can be mapped to chromosomes by preparing PCR primers (preferably at least 15 bp (e.g., 15-25 bp) from the sequences shown in SEQ ID NO:X.

Primers can optionally be selected using computer analysis so that primers do not span more than one predicted exon in the genomic DNA. These primers are then used for PCR screening of somatic cell hybrids containing individual human chromosomes. Only those hybrids containing the human gene corresponding to SEQ ID NO:X will yield an amplified fragment.

[464] Similarly, somatic hybrids provide a rapid method of PCR mapping the polynucleotides to particular chromosomes. Three or more clones can be assigned per day using a single thermal cycler. Moreover, sublocalization of the polynucleotides can be achieved with panels of specific chromosome fragments. Other gene mapping strategies that can be used include in situ hybridization, prescreening with labeled flow-sorted chromosomes, preselection by hybridization to construct chromosome specific-cDNA libraries, and computer mapping techniques (See, e.g., Shuler, Trends Biotechnol 16:456-459 (1998) which is hereby incorporated by reference in its entirety).

[465] Precise chromosomal location of the polynucleotides can also be achieved using fluorescence in situ hybridization (FISH) of a metaphase chromosomal spread. This technique uses polynucleotides as short as 500 or 600 bases; however, polynucleotides 2,000-4,000 bp are preferred. For a review of this technique, see Verma et al., "Human Chromosomes: a Manual of Basic Techniques," Pergamon Press, New York (1988).

[466] For chromosome mapping, the polynucleotides can be used individually (to mark a single chromosome or a single site on that chromosome) or in panels (for marking multiple sites and/or multiple chromosomes).

[467] Thus, the present invention also provides a method for chromosomal localization which involves (a) preparing PCR primers from the polynucleotide sequences in Table 1 and SEQ ID NO:X and (b) screening somatic cell hybrids containing individual chromosomes.

[468] The polynucleotides of the present invention would likewise be useful for radiation hybrid mapping, HAPPY mapping, and long range restriction mapping. For a review of these techniques and others known in the art, see, e.g. Dear, "Genome Mapping: A Practical Approach," IRL Press at Oxford University Press, London (1997); Aydin, J. Mol. Med. 77:691-694 (1999); Hacia et al., Mol. Psychiatry 3:483-492 (1998); Herrick et al., Chromosome Res. 7:409-423 (1999); Hamilton et al., Methods Cell Biol. 62:265-280 (2000); and/or Ott, J. Hered. 90:68-70 (1999) each of which is hereby incorporated by reference in its entirety.

[469] Once a polynucleotide has been mapped to a precise chromosomal location, the physical position of the polynucleotide can be used in linkage analysis. Linkage analysis establishes coinheritance between a chromosomal location and presentation of a particular disease. (Disease mapping data are found, for example, in V. McKusick, Mendelian Inheritance in Man (available on line through Johns Hopkins University Welch Medical Library)). Assuming 1 megabase mapping resolution and one gene per 20 kb, a cDNA precisely localized to a chromosomal region associated with the disease could be one of 50-500 potential causative genes.

[470] Thus, once coinheritance is established, differences in a polynucleotide of the invention and the corresponding gene between affected and unaffected individuals can be examined. First, visible structural alterations in the chromosomes, such as deletions or translocations, are examined in chromosome spreads or by PCR. If no structural alterations exist, the presence of point mutations are ascertained. Mutations observed in some or all affected individuals, but not in normal individuals, indicates that the mutation may cause the disease. However, complete sequencing of the polypeptide and the corresponding gene from several normal individuals is required to distinguish the mutation from a polymorphism. If a new polymorphism is identified, this polymorphic polypeptide can be used for further linkage analysis.

[471] Furthermore, increased or decreased expression of the gene in affected individuals as compared to unaffected individuals can be assessed using the polynucleotides of the invention. Any of these alterations (altered expression, chromosomal rearrangement, or mutation) can be used as a diagnostic or prognostic marker.

[472] Thus, the invention also provides a diagnostic method useful during diagnosis of a disorder, involving measuring the expression level of polynucleotides of the present invention in cells or body fluid from an individual and comparing the measured gene expression level with a standard level of polynucleotide expression level, whereby an increase or decrease in the gene expression level compared to the standard is indicative of a disorder.

[473] In still another embodiment, the invention includes a kit for analyzing samples for the presence of proliferative and/or cancerous polynucleotides derived from a test subject. In a general embodiment, the kit includes at least one polynucleotide probe containing a nucleotide sequence that will specifically hybridize with a polynucleotide of the invention and a suitable container. In a specific embodiment, the kit includes two polynucleotide probes

defining an internal region of the polynucleotide of the invention, where each probe has one strand containing a 31'mer-end internal to the region. In a further embodiment, the probes may be useful as primers for polymerase chain reaction amplification.

[474] Where a diagnosis of a related disorder, including, for example, diagnosis of a tumor, has already been made according to conventional methods, the present invention is useful as a prognostic indicator, whereby patients exhibiting enhanced or depressed polynucleotide of the invention expression will experience a worse clinical outcome relative to patients expressing the gene at a level nearer the standard level.

[475] By "measuring the expression level of polynucleotides of the invention" is intended qualitatively or quantitatively measuring or estimating the level of the polypeptide of the invention or the level of the mRNA encoding the polypeptide of the invention in a first biological sample either directly (e.g., by determining or estimating absolute protein level or mRNA level) or relatively (e.g., by comparing to the polypeptide level or mRNA level in a second biological sample). Preferably, the polypeptide level or mRNA level in the first biological sample is measured or estimated and compared to a standard polypeptide level or mRNA level, the standard being taken from a second biological sample obtained from an individual not having the related disorder or being determined by averaging levels from a population of individuals not having a related disorder. As will be appreciated in the art, once a standard polypeptide level or mRNA level is known, it can be used repeatedly as a standard for comparison.

[476] By "biological sample" is intended any biological sample obtained from an individual, body fluid, cell line, tissue culture, or other source which contains polypeptide of the present invention or the corresponding mRNA. As indicated, biological samples include body fluids (such as semen, lymph, sera, plasma, urine, synovial fluid and spinal fluid) which contain the polypeptide of the present invention, and tissue sources found to express the polypeptide of the present invention. Methods for obtaining tissue biopsies and body fluids from mammals are well known in the art. Where the biological sample is to include mRNA, a tissue biopsy is the preferred source.

[477] The method(s) provided above may preferrably be applied in a diagnostic method and/or kits in which polynucleotides and/or polypeptides of the invention are attached to a solid support. In one exemplary method, the support may be a "gene chip" or a "biological chip" as described in US Patents 5,837,832, 5,874,219, and 5,856,174. Further, such a gene

chip with polynucleotides of the invention attached may be used to identify polymorphisms between the isolated polynucleotide sequences of the invention, with polynucleotides isolated from a test subject. The knowledge of such polymorphisms (i.e. their location, as well as, their existence) would be beneficial in identifying disease loci for many disorders, such as for example, in neural disorders, immune system disorders, muscular disorders, reproductive disorders, gastrointestinal disorders, pulmonary disorders, cardiovascular disorders, renal disorders, proliferative disorders, and/or cancerous diseases and conditions. Such a method is described in US Patents 5,858,659 and 5,856,104. The US Patents referenced supra are hereby incorporated by reference in their entirety herein.

[478] The present invention encompasses polynucleotides of the present invention that are chemically synthesized, or reproduced as peptide nucleic acids (PNA), or according to other methods known in the art. The use of PNAs would serve as the preferred form if the polynucleotides of the invention are incorporated onto a solid support, or gene chip. For the purposes of the present invention, a peptide nucleic acid (PNA) is a polyamide type of DNA analog and the monomeric units for adenine, guanine, thymine and cytosine are available commercially (Perceptive Biosystems). Certain components of DNA, such as phosphorus, phosphorus oxides, or deoxyribose derivatives, are not present in PNAs. As disclosed by P. E. Nielsen, M. Egholm, R. H. Berg and O. Buchardt, Science 254, 1497 (1991); and M. Egholm, O. Buchardt, L.Christensen, C. Behrens, S. M. Freier, D. A. Driver, R. H. Berg, S. K. Kim, B. Norden, and P. E. Nielsen, Nature 365, 666 (1993), PNAs bind specifically and tightly to complementary DNA strands and are not degraded by nucleases. In fact, PNA binds more strongly to DNA than DNA itself does. This is probably because there is no electrostatic repulsion between the two strands, and also the polyamide backbone is more flexible. Because of this, PNA/DNA duplexes bind under a wider range of stringency conditions than DNA/DNA duplexes, making it easier to perform multiplex hybridization. Smaller probes can be used than with DNA due to the strong binding. In addition, it is more likely that single base mismatches can be determined with PNA/DNA hybridization because a single mismatch in a PNA/DNA 15-mer lowers the melting point (T.sub.m) by 8°-20° C, vs. 4°-16° C for the DNA/DNA 15-mer duplex. Also, the absence of charge groups in PNA means that hybridization can be done at low ionic strengths and reduce possible interference by salt during the analysis.

[479] The present invention have uses which include, but are not limited to, detecting cancer in mammals. In particular the invention is useful during diagnosis of pathological cell proliferative neoplasias which include, but are not limited to: acute myelogenous leukemias including acute monocytic leukemia, acute myeloblastic leukemia, acute promyelocytic leukemia, acute myelomonocytic leukemia, acute erythroleukemia, acute megakaryocytic leukemia, and acute undifferentiated leukemia, etc.; and chronic myelogenous leukemias including chronic myelomonocytic leukemia, chronic granulocytic leukemia, etc. Preferred mammals include monkeys, apes, cats, dogs, cows, pigs, horses, rabbits and humans. Particularly preferred are humans.

[480] Pathological cell proliferative disorders are often associated with inappropriate activation of proto-oncogenes. (Gelmann, E. P. et al., "The Etiology of Acute Leukemia: Molecular Genetics and Viral Oncology," in Neoplastic Diseases of the Blood, Vol 1., Wiernik, P. H. et al. eds., 161-182 (1985)). Neoplasias are now believed to result from the qualitative alteration of a normal cellular gene product, or from the quantitative modification of gene expression by insertion into the chromosome of a viral sequence, by chromosomal translocation of a gene to a more actively transcribed region, or by some other mechanism. (Gelmann et al., supra) It is likely that mutated or altered expression of specific genes is involved in the pathogenesis of some leukemias, among other tissues and cell types. (Gelmann et al., supra) Indeed, the human counterparts of the oncogenes involved in some animal neoplasias have been amplified or translocated in some cases of human leukemia and carcinoma. (Gelmann et al., supra)

[481] For example, c-myc expression is highly amplified in the non-lymphocytic leukemia cell line HL-60. When HL-60 cells are chemically induced to stop proliferation, the level of c-myc is found to be downregulated. (International Publication Number WO 91/15580). However, it has been shown that exposure of HL-60 cells to a DNA construct that is complementary to the 5' end of c-myc or c-myb blocks translation of the corresponding mRNAs which downregulates expression of the c-myc or c-myb proteins and causes arrest of cell proliferation and differentiation of the treated cells. (International Publication Number WO 91/15580; Wickstrom et al., Proc. Natl. Acad. Sci. 85:1028 (1988); Anfossi et al., Proc. Natl. Acad. Sci. 86:3379 (1989)). However, the skilled artisan would appreciate the present invention's usefulness is not be limited to treatment of proliferative disorders of

hematopoietic cells and tissues, in light of the numerous cells and cell types of varying origins which are known to exhibit proliferative phenotypes.

[482] In addition to the foregoing, a polynucleotide of the present invention can be used to control gene expression through triple helix formation or through antisense DNA or RNA. Antisense techniques are discussed, for example, in Okano, J. Neurochem. 56: 560 (1991); "Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Triple helix formation is discussed in, for instance Lee et al., Nucleic Acids Research 6: 3073 (1979); Cooney et al., Science 241: 456 (1988); and Dervan et al., Science 251: 1360 (1991). Both methods rely on binding of the polynucleotide to a complementary DNA or RNA. For these techniques, preferred polynucleotides are usually oligonucleotides 20 to 40 bases in length and complementary to either the region of the gene involved in transcription (triple helix - see Lee et al., Nucl. Acids Res. 6:3073 (1979); Cooney et al., Science 241:456 (1988); and Dervan et al., Science 251:1360 (1991)) or to the mRNA itself (antisense - Okano, J. Neurochem. 56:560 (1991); Oligodeoxy-nucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988)). Triple helix formation optimally results in a shut-off of RNA transcription from DNA, while antisense RNA hybridization blocks translation of an mRNA molecule into polypeptide. The oligonucleotide described above can also be delivered to cells such that the antisense RNA or DNA may be expressed in vivo to inhibit production of polypeptide of the present invention antigens. Both techniques are effective in model systems, and the information disclosed herein can be used to design antisense or triple helix polynucleotides in an effort to treat disease, and in particular, for the treatment of proliferative diseases and/or conditions.

[483] Polynucleotides of the present invention are also useful in gene therapy. One goal of gene therapy is to insert a normal gene into an organism having a defective gene, in an effort to correct the genetic defect. The polynucleotides disclosed in the present invention offer a means of targeting such genetic defects in a highly accurate manner. Another goal is to insert a new gene that was not present in the host genome, thereby producing a new trait in the host cell.

[484] The polynucleotides are also useful for identifying individuals from minute biological samples. The United States military, for example, is considering the use of restriction fragment length polymorphism (RFLP) for identification of its personnel. In this technique, an individual's genomic DNA is digested with one or more restriction enzymes,

and probed on a Southern blot to yield unique bands for identifying personnel. This method does not suffer from the current limitations of "Dog Tags" which can be lost, switched, or stolen, making positive identification difficult. The polynucleotides of the present invention can be used as additional DNA markers for RFLP.

[485] The polynucleotides of the present invention can also be used as an alternative to RFLP, by determining the actual base-by-base DNA sequence of selected portions of an individual's genome. These sequences can be used to prepare PCR primers for amplifying and isolating such selected DNA, which can then be sequenced. Using this technique, individuals can be identified because each individual will have a unique set of DNA sequences. Once an unique ID database is established for an individual, positive identification of that individual, living or dead, can be made from extremely small tissue samples.

[486] Forensic biology also benefits from using DNA-based identification techniques as disclosed herein. DNA sequences taken from very small biological samples such as tissues, e.g., hair or skin, or body fluids, e.g., blood, saliva, semen, synovial fluid, amniotic fluid, breast milk, lymph, pulmonary sputum or surfactant, urine, fecal matter, etc., can be amplified using PCR. In one prior art technique, gene sequences amplified from polymorphic loci, such as DQa class II HLA gene, are used in forensic biology to identify individuals. (Erlich, H., PCR Technology, Freeman and Co. (1992)). Once these specific polymorphic loci are amplified, they are digested with one or more restriction enzymes, yielding an identifying set of bands on a Southern blot probed with DNA corresponding to the DQa class II HLA gene. Similarly, polynucleotides of the present invention can be used as polymorphic markers for forensic purposes.

[487] There is also a need for reagents capable of identifying the source of a particular tissue. Such need arises, for example, in forensics when presented with tissue of unknown origin. Appropriate reagents can comprise, for example, DNA probes or primers prepared from the sequences of the present invention. Panels of such reagents can identify tissue by species and/or by organ type. In a similar fashion, these reagents can be used to screen tissue cultures for contamination.

[488] The polynucleotides of the present invention are also useful as hybridization probes for differential identification of the tissue(s) or cell type(s) present in a biological sample. Similarly, polypeptides and antibodies directed to polypeptides of the present

invention are useful to provide immunological probes for differential identification of the tissue(s) (e.g., immunohistochemistry assays) or cell type(s) (e.g., immunocytochemistry assays). In addition, for a number of disorders of the above tissues or cells, significantly higher or lower levels of gene expression of the polynucleotides/polypeptides of the present invention may be detected in certain tissues (e.g., tissues expressing polypeptides and/or polynucleotides of the present invention and/or cancerous and/or wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to a "standard" gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

[489] Thus, the invention provides a diagnostic method of a disorder, which involves: (a) assaying gene expression level in cells or body fluid of an individual; (b) comparing the gene expression level with a standard gene expression level, whereby an increase or decrease in the assayed gene expression level compared to the standard expression level is indicative of a disorder.

[490] In the very least, the polynucleotides of the present invention can be used as molecular weight markers on Southern gels, as diagnostic probes for the presence of a specific mRNA in a particular cell type, as a probe to "subtract-out" known sequences in the process of discovering novel polynucleotides, for selecting and making oligomers for attachment to a "gene chip" or other support, to raise anti-DNA antibodies using DNA immunization techniques, and as an antigen to elicit an immune response.

Uses of the Polypeptides

[491] Each of the polypeptides identified herein can be used in numerous ways. The following description should be considered exemplary and utilizes known techniques.

[492] Polypeptides and antibodies directed to polypeptides of the present invention are useful to provide immunological probes for differential identification of the tissue(s) (e.g., immunohistochemistry assays such as, for example, ABC immunoperoxidase (Hsu et al., J. Histochem. Cytochem. 29:577-580 (1981)) or cell type(s) (e.g., immunocytochemistry assays).

[493] Antibodies can be used to assay levels of polypeptides encoded by polynucleotides of the invention in a biological sample using classical immunohistological methods known to those of skill in the art (e.g., see Jalkanen, et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen,

et al., J. Cell. Biol. 105:3087-3096 (1987)). Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase; radioisotopes, such as iodine (^{131}I, ^{125}I, ^{123}I, ^{121}I), carbon (^{14}C), sulfur (^{35}S), tritium (^{3}H), indium (^{115m}In, ^{113m}In, ^{112}In, ^{111}In), and technetium (^{99}Tc, ^{99m}Tc), thallium (^{201}Ti), gallium (^{68}Ga, ^{67}Ga), palladium (^{103}Pd), molybdenum (^{99}Mo), xenon (^{133}Xe), fluorine (^{18}F), ^{153}Sm, ^{177}Lu, ^{159}Gd, ^{149}Pm, ^{140}La, ^{175}Yb, ^{166}Ho, ^{90}Y, ^{47}Sc, ^{186}Re, ^{188}Re, ^{142}Pr, ^{105}Rh, ^{97}Ru; luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

[494] In addition to assaying levels of polypeptide of the present invention in a biological sample, proteins can also be detected in vivo by imaging. Antibody labels or markers for in vivo imaging of protein include those detectable by X-radiography, NMR or ESR. For X-radiography, suitable labels include radioisotopes such as barium or cesium, which emit detectable radiation but are not overtly harmful to the subject. Suitable markers for NMR and ESR include those with a detectable characteristic spin, such as deuterium, which may be incorporated into the antibody by labeling of nutrients for the relevant hybridoma.

[495] A protein-specific antibody or antibody fragment which has been labeled with an appropriate detectable imaging moiety, such as a radioisotope (for example, ^{131}I, ^{112}In, ^{99m}Tc, (^{131}I, ^{125}I, ^{123}I, ^{121}I), carbon (^{14}C), sulfur (^{35}S), tritium (^{3}H), indium (^{115m}In, ^{113m}In, ^{112}In, ^{111}In), and technetium (^{99}Tc, ^{99m}Tc), thallium (^{201}Ti), gallium (^{68}Ga, ^{67}Ga), palladium (^{103}Pd), molybdenum (^{99}Mo), xenon (^{133}Xe), fluorine (^{18}F, ^{153}Sm, ^{177}Lu, ^{159}Gd, ^{149}Pm, ^{140}La, ^{175}Yb, ^{166}Ho, ^{90}Y, ^{47}Sc, ^{186}Re, ^{188}Re, ^{142}Pr, ^{105}Rh, ^{97}Ru), a radio-opaque substance, or a material detectable by nuclear magnetic resonance, is introduced (for example, parenterally, subcutaneously or intraperitoneally) into the mammal to be examined for immune system disorder. It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of ^{99m}Tc. The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which express the polypeptide encoded by a polynucleotide of the invention. *In vivo* tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and

Their Fragments" (Chapter 13 in *Tumor Imaging: The Radiochemical Detection of Cancer*, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982)).

[496] In one embodiment, the invention provides a method for the specific delivery of compositions of the invention to cells by administering polypeptides of the invention (e.g., polypeptides encoded by polynucleotides of the invention and/or antibodies) that are associated with heterologous polypeptides or nucleic acids. In one example, the invention provides a method for delivering a therapeutic protein into the targeted cell. In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., antisense or ribozymes) or double stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate episomally and that can be transcribed) into the targeted cell.

[497] In another embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention in association with toxins or cytotoxic prodrugs.

[498] By "toxin" is meant one or more compounds that bind and activate endogenous cytotoxic effector systems, radioisotopes, holotoxins, modified toxins, catalytic subunits of toxins, or any molecules or enzymes not normally present in or on the surface of a cell that under defined conditions cause the cell's death. Toxins that may be used according to the methods of the invention include, but are not limited to, radioisotopes known in the art, compounds such as, for example, antibodies (or complement fixing containing portions thereof) that bind an inherent or induced endogenous cytotoxic effector system, thymidine kinase, endonuclease, RNAse, alpha toxin, ricin, abrin, *Pseudomonas* exotoxin A, diphtheria toxin, saporin, momordin, gelonin, pokeweed antiviral protein, alpha-sarcin and cholera toxin. "Toxin" also includes a cytostatic or cytocidal agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example, ^{213}Bi, or other radioisotopes such as, for example, ^{103}Pd, ^{133}Xe, ^{131}I, ^{68}Ge, ^{57}Co, ^{65}Zn, ^{85}Sr, ^{32}P, ^{35}S, ^{90}Y, ^{153}Sm, ^{153}Gd, ^{169}Yb, ^{51}Cr, ^{54}Mn, ^{75}Se, ^{113}Sn, ^{90}Yttrium, ^{117}Tin, ^{186}Rhenium, ^{166}Holmium, and ^{188}Rhenium; luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

[499] Techniques known in the art may be applied to label polypeptides of the invention (including antibodies). Such techniques include, but are not limited to, the use of bifunctional conjugating agents (see e.g., U.S. Patent Nos. 5,756,065; 5,714,631; 5,696,239; 5,652,361; 5,505,931; 5,489,425; 5,435,990; 5,428,139; 5,342,604; 5,274,119; 4,994,560;

and 5,808,003; the contents of each of which are hereby incorporated by reference in its entirety).

[500] Thus, the invention provides a diagnostic method of a disorder, which involves (a) assaying the expression level of a polypeptide of the present invention in cells or body fluid of an individual; and (b) comparing the assayed polypeptide expression level with a standard polypeptide expression level, whereby an increase or decrease in the assayed polypeptide expression level compared to the standard expression level is indicative of a disorder. With respect to cancer, the presence of a relatively high amount of transcript in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

[501] Moreover, polypeptides of the present invention can be used to treat or prevent diseases or conditions such as, for example, neural disorders, immune system disorders, muscular disorders, reproductive disorders, gastrointestinal disorders, pulmonary disorders, cardiovascular disorders, renal disorders, proliferative disorders, and/or cancerous diseases and conditions. For example, patients can be administered a polypeptide of the present invention in an effort to replace absent or decreased levels of the polypeptide (e.g., insulin), to supplement absent or decreased levels of a different polypeptide (e.g., hemoglobin S for hemoglobin B, SOD, catalase, DNA repair proteins), to inhibit the activity of a polypeptide (e.g., an oncogene or tumor supressor), to activate the activity of a polypeptide (e.g., by binding to a receptor), to reduce the activity of a membrane bound receptor by competing with it for free ligand (e.g., soluble TNF receptors used in reducing inflammation), or to bring about a desired response (e.g., blood vessel growth inhibition, enhancement of the immune response to proliferative cells or tissues).

[502] Similarly, antibodies directed to a polypeptide of the present invention can also be used to treat disease (as described supra, and elsewhere herein). For example, administration of an antibody directed to a polypeptide of the present invention can bind, and/or neutralize the polypeptide, and/or reduce overproduction of the polypeptide. Similarly, administration of an antibody can activate the polypeptide, such as by binding to a polypeptide bound to a membrane (receptor).

[503] At the very least, the polypeptides of the present invention can be used as molecular weight markers on SDS-PAGE gels or on molecular sieve gel filtration columns using methods well known to those of skill in the art. Polypeptides can also be used to raise antibodies, which in turn are used to measure protein expression from a recombinant cell, as a way of assessing transformation of the host cell. Moreover, the polypeptides of the present invention can be used to test the following biological activities.

Diagnostic Assays

[504] The compounds of the present invention are useful for diagnosis, treatment, prevention and/or prognosis of various disorders in mammals, preferably humans. Such disorders include, but are not limited to, neural disorders (e.g., as described in "Neural Activity and Neurological Diseases" below), immune system disorders (e.g., as described in "Immune Activity" below), muscular disorders (e.g., as described in "Neural Activity and Neurological Diseases" below), reproductive disorders (e.g., as described in "Anti-Angiogenesis Activity" below), pulmonary disorders (e.g., as described in "Immune Activity" below), cardiovascular disorders (e.g., as described in "Cardiovascular Disorders" below), infectious diseases (e.g., as described in "Infectious Disease" below), proliferative disorders (e.g., as described in "Hyperproliferative Disorders", "Anti-Angiogenesis Activity" and "Diseases at the Cellular Level" below), and/or cancerous diseases and conditions (e.g., as described in "Hyperproliferative Disorders", "Anti-Angiogenesis Activity" and "Diseases at the Cellular Level" below).

[505] Members of the B7-like family of proteins are believed to be involved in biological activities associated with T cell activation, cytokine production, T cell proliferation, and immune system and inflammatory disorders. Accordingly, compositions of the invention (including polynucleotides, polypeptides and antibodies of the invention, and fragments and variants thereof) may be used in the diagnosis, detection and/or treatment of diseases and/or disorders associated with aberrant B7-like activities.

[506] In preferred embodiments, compositions of the invention (including polynucleotides, polypeptides and antibodies of the invention, and fragments and variants thereof) may be used in the diagnosis, detection and/or treatment of diseases and/or disorders relating to the immune system in general, and T cell activation specifically (e.g., cytokine production, inflammation, T cell proliferation and T cell proliferative disorders, and/or as

described under "Immune Activity", "Hyperproliferative Disorders" and "Diseases at the Cellular Level" below).

[507] In another embodiment, a polypeptide of the invention, or polynucleotides, antibodies, agonists, or antagonists corresponding to that polypeptide, may be used to diagnose, prognose, prevent, and/or treat disorders associated with the tissue(s) in which the polypeptide of the invention is expressed, including the tissues disclosed in "Polynucleotides and Polypeptides of the Invention", and/or one, two, three, four, five, or more tissues disclosed in Table 10, column 2 (Library Code).

[508] For a number of disorders, substantially altered (increased or decreased) levels of B7-like gene expression can be detected in tissues, cells or bodily fluids (e.g., sera, plasma, urine, semen, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to a "standard" B7-like gene expression level, that is, the B7-like expression level in tissues or bodily fluids from an individual not having the disorder. Thus, the invention provides a diagnostic method useful during diagnosis of a disorder, which involves measuring the expression level of the gene encoding the B7-like polypeptide in tissues, cells or body fluid from an individual and comparing the measured gene expression level with a standard B7-like gene expression level, whereby an increase or decrease in the gene expression level(s) compared to the standard is indicative of a B7-like disorder. These diagnostic assays may be performed *in vivo* or *in vitro*, such as, for example, on blood samples, biopsy tissue or autopsy tissue.

[509] The present invention is also useful as a prognostic indicator, whereby patients exhibiting enhanced or depressed B7-like gene expression will experience a worse clinical outcome relative to patients expressing the gene at a level nearer the standard level.

[510] By "assaying the expression level of the gene encoding the B7-like polypeptide" is intended qualitatively or quantitatively measuring or estimating the level of the B7-like polypeptide or the level of the mRNA encoding the B7-like polypeptide in a first biological sample either directly (e.g., by determining or estimating absolute protein level or mRNA level) or relatively (e.g., by comparing to the B7-like polypeptide level or mRNA level in a second biological sample). Preferably, the B7-like polypeptide expression level or mRNA level in the first biological sample is measured or estimated and compared to a standard B7-like polypeptide level or mRNA level, the standard being taken from a second biological sample obtained from an individual not having the disorder or being determined by averaging

levels from a population of individuals not having the disorder. As will be appreciated in the art, once a standard B7-like polypeptide level or mRNA level is known, it can be used repeatedly as a standard for comparison.

[511] By "biological sample" is intended any biological sample obtained from an individual, cell line, tissue culture, or other source containing B7-like polypeptides (including portions thereof) or mRNA. As indicated, biological samples include body fluids (such as sera, plasma, urine, synovial fluid and spinal fluid) and tissue sources found to express the full length or fragments thereof of a B7-like polypeptide. Methods for obtaining tissue biopsies and body fluids from mammals are well known in the art. Where the biological sample is to include mRNA, a tissue biopsy is the preferred source.

[512] Total cellular RNA can be isolated from a biological sample using any suitable technique such as the single-step guanidinium-thiocyanate-phenol-chloroform method described in Chomczynski and Sacchi, Anal. Biochem. 162:156-159 (1987). Levels of mRNA encoding the B7-like polypeptides are then assayed using any appropriate method. These include Northern blot analysis, S1 nuclease mapping, the polymerase chain reaction (PCR), reverse transcription in combination with the polymerase chain reaction (RT-PCR), and reverse transcription in combination with the ligase chain reaction (RT-LCR).

[513] The present invention also relates to diagnostic assays such as quantitative and diagnostic assays for detecting levels of B7-like polypeptides, in a biological sample (e.g., cells and tissues), including determination of normal and abnormal levels of polypeptides. Thus, for instance, a diagnostic assay in accordance with the invention for detecting over-expression of B7-like polypeptides compared to normal control tissue samples may be used to detect the presence of tumors. Assay techniques that can be used to determine levels of a polypeptide, such as a B7-like polypeptide of the present invention in a sample derived from a host are well-known to those of skill in the art. Such assay methods include radioimmunoassays, competitive-binding assays, Western Blot analysis and ELISA assays. Assaying B7-like polypeptide levels in a biological sample can occur using any art-known method.

[514] Assaying B7-like polypeptide levels in a biological sample can occur using antibody-based techniques. For example, B7-like polypeptide expression in tissues can be studied with classical immunohistological methods (Jalkanen et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, M., et al., *J. Cell Biol.*, 105:3087-3096 (1987)). Other

antibody-based methods useful for detecting B7-like polypeptide gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase, and radioisotopes, such as iodine (^{125}I, ^{121}I), carbon (^{14}C), sulfur (^{35}S), tritium (^{3}H), indium (^{112}In), and technetium (^{99m}Tc), and fluorescent labels, such as fluorescein and rhodamine, and biotin.

[515] The tissue or cell type to be analyzed will generally include those which are known, or suspected, to express the B7-like gene (such as, for example, cancer). The protein isolation methods employed herein may, for example, be such as those described in Harlow and Lane (Harlow, E. and Lane, D., 1988, "Antibodies: A Laboratory Manual", Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York), which is incorporated herein by reference in its entirety. The isolated cells can be derived from cell culture or from a patient. The analysis of cells taken from culture may be a necessary step in the assessment of cells that could be used as part of a cell-based gene therapy technique or, alternatively, to test the effect of compounds on the expression of the B7-like gene.

[516] For example, antibodies, or fragments of antibodies, such as those described herein, may be used to quantitatively or qualitatively detect the presence of B7-like gene products or conserved variants or peptide fragments thereof. This can be accomplished, for example, by immunofluorescence techniques employing a fluorescently labeled antibody coupled with light microscopic, flow cytometric, or fluorimetric detection.

[517] In a preferred embodiment, antibodies, or fragments of antibodies directed to any one or all of the predicted epitope domains of the B7-like polypeptides may be used to quantitatively or qualitatively detect the presence of B7-like gene products or conserved variants or peptide fragments thereof. This can be accomplished, for example, by immunofluorescence techniques employing a fluorescently labeled antibody coupled with light microscopic, flow cytometric, or fluorimetric detection.

[518] In an additional preferred embodiment, antibodies, or fragments of antibodies directed to a conformational epitope of a B7-like polypeptide may be used to quantitatively or qualitatively detect the presence of B7-like gene products or conserved variants or peptide fragments thereof. This can be accomplished, for example, by immunofluorescence techniques employing a fluorescently labeled antibody coupled with light microscopic, flow cytometric, or fluorimetric detection.

[519] The antibodies (or fragments thereof), and/or B7-like polypeptides of the present invention may, additionally, be employed histologically, as in immunofluorescence, immunoelectron microscopy or non-immunological assays, for in situ detection of B7-like gene products or conserved variants or peptide fragments thereof. In situ detection may be accomplished by removing a histological specimen from a patient, and applying thereto a labeled antibody or B7-like polypeptide of the present invention. The antibody (or fragment thereof) or B7-like polypeptide is preferably applied by overlaying the labeled antibody (or fragment) onto a biological sample. Through the use of such a procedure, it is possible to determine not only the presence of the B7-like gene product, or conserved variants or peptide fragments, or B7-like polypeptide binding, but also its distribution in the examined tissue. Using the present invention, those of ordinary skill will readily perceive that any of a wide variety of histological methods (such as staining procedures) can be modified in order to achieve such in situ detection.

[520] Immunoassays and non-immunoassays for B7-like gene products or conserved variants or peptide fragments thereof will typically comprise incubating a sample, such as a biological fluid, a tissue extract, freshly harvested cells, or lysates of cells which have been incubated in cell culture, in the presence of a detectably labeled antibody capable of binding B7-like gene products or conserved variants or peptide fragments thereof, and detecting the bound antibody by any of a number of techniques well-known in the art.

[521] The biological sample may be brought in contact with and immobilized onto a solid phase support or carrier such as nitrocellulose, or other solid support which is capable of immobilizing cells, cell particles or soluble proteins. The support may then be washed with suitable buffers followed by treatment with the detectably labeled anti-B7-like polypeptide antibody or detectable B7-like polypeptide. The solid phase support may then be washed with the buffer a second time to remove unbound antibody or polypeptide. Optionally the antibody is subsequently labeled. The amount of bound label on solid support may then be detected by conventional means.

[522] By "solid phase support or carrier" is intended any support capable of binding an antigen or an antibody. Well-known supports or carriers include glass, polystyrene, polypropylene, polyethylene, dextran, nylon, amylases, natural and modified celluloses, polyacrylamides, gabbros, and magnetite. The nature of the carrier can be either soluble to some extent or insoluble for the purposes of the present invention. The support material may

have virtually any possible structural configuration so long as the coupled molecule is capable of binding to an antigen or antibody. Thus, the support configuration may be spherical, as in a bead, or cylindrical, as in the inside surface of a test tube, or the external surface of a rod. Alternatively, the surface may be flat such as a sheet, test strip, etc. Preferred supports include polystyrene beads. Those skilled in the art will know many other suitable carriers for binding antibody or antigen, or will be able to ascertain the same by use of routine experimentation.

[523] The binding activity of a given lot of anti-B7-like polypeptide antibody or B7-like antigen polypeptide may be determined according to well known methods. Those skilled in the art will be able to determine operative and optimal assay conditions for each determination by employing routine experimentation.

[524] In addition to assaying B7-like polypeptide levels or polynucleotide levels in a biological sample obtained from an individual, B7-like polypeptide or polynucleotide can also be detected *in vivo* by imaging. For example, in one embodiment of the invention, B7-like polypeptide and/or anti-B7-like antigen antibodies are used to image diseased cells, such as neoplasms. In another embodiment, B7-like polynucleotides of the invention (e.g., polynucleotides complementary to all or a portion of a particular B7-like mRNA transcript) and/or anti-B7-like antibodies (e.g., antibodies directed to any one or a combination of the epitopes of a B7-like polypeptide of the invention, antibodies directed to a conformational epitope of a B7-like polypeptide of the invention, or antibodies directed to the full length polypeptide expressed on the cell surface of a mammalian cell) are used to image diseased or neoplastic cells.

[525] Antibody labels or markers for *in vivo* imaging of B7-like polypeptides include those detectable by X-radiography, NMR, MRI, CAT-scans or ESR. For X-radiography, suitable labels include radioisotopes such as barium or cesium, which emit detectable radiation but are not overtly harmful to the subject. Suitable markers for NMR and ESR include those with a detectable characteristic spin, such as deuterium, which may be incorporated into the antibody by labeling of nutrients for the relevant hybridoma. Where *in vivo* imaging is used to detect enhanced levels of B7-like polypeptides for diagnosis in humans, it may be preferable to use human antibodies or "humanized" chimeric monoclonal antibodies. Such antibodies can be produced using techniques described herein or otherwise known in the art. For example methods for producing chimeric antibodies are known in the

art. See, for review, Morrison, *Science 229*:1202 (1985); Oi et al., *BioTechniques 4*:214 (1986); Cabilly et al.,. U.S. Patent No. 4,816,567; Taniguchi et al., EP 171496; Morrison et al., EP 173494; Neuberger et al., WO 8601533; Robinson et al., WO 8702671; Boulianne *et al., Nature 312*:643 (1984); Neuberger *et al., Nature 314*:268 (1985).

[526] Additionally, any B7-like polypeptides whose presence can be detected, can be administered. For example, B7-like polypeptides labeled with a radio-opaque or other appropriate compound can be administered and visualized *in vivo*, as discussed, above for labeled antibodies. Further such B7-like polypeptides can be utilized for *in vitro* diagnostic procedures.

[527] A B7-like polypeptide-specific antibody or antibody fragment which has been labeled with an appropriate detectable imaging moiety, such as a radioisotope (for example, ^{131}I, ^{112}In, ^{99m}Tc), a radio-opaque substance, or a material detectable by nuclear magnetic resonance, is introduced (for example, parenterally, subcutaneously or intraperitoneally) into the mammal to be examined for a disorder. It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of ^{99m}Tc. The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which contain B7-like protein. *In vivo* tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments" (Chapter 13 in *Tumor Imaging: The Radiochemical Detection of Cancer*, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982)).

[528] With respect to antibodies, one of the ways in which the anti-B7-like polypeptide antibody can be detectably labeled is by linking the same to a reporter enzyme and using the linked product in an enzyme immunoassay (EIA) (Voller, A., "The Enzyme Linked Immunosorbent Assay (ELISA)", 1978, Diagnostic Horizons 2:1-7, Microbiological Associates Quarterly Publication, Walkersville, MD); Voller et al., *J. Clin. Pathol.* 31:507-520 (1978); Butler, J.E., *Meth. Enzymol.* 73:482-523 (1981); Maggio, E. (ed.), 1980, Enzyme Immunoassay, CRC Press, Boca Raton, FL,; Ishikawa, E. et al., (eds.), 1981, Enzyme Immunoassay, Kgaku Shoin, Tokyo). The reporter enzyme which is bound to the antibody will react with an appropriate substrate, preferably a chromogenic substrate, in such a manner as to produce a chemical moiety which can be detected, for example, by spectrophotometric,

fluorimetric or by visual means. Reporter enzymes which can be used to detectably label the antibody include, but are not limited to, malate dehydrogenase, staphylococcal nuclease, delta-5-steroid isomerase, yeast alcohol dehydrogenase, alpha-glycerophosphate, dehydrogenase, triose phosphate isomerase, horseradish peroxidase, alkaline phosphatase, asparaginase, glucose oxidase, beta-galactosidase, ribonuclease, urease, catalase, glucose-6-phosphate dehydrogenase, glucoamylase and acetylcholinesterase. Additionally, the detection can be accomplished by colorimetric methods which employ a chromogenic substrate for the reporter enzyme. Detection may also be accomplished by visual comparison of the extent of enzymatic reaction of a substrate in comparison with similarly prepared standards.

[529] Detection may also be accomplished using any of a variety of other immunoassays. For example, by radioactively labeling the antibodies or antibody fragments, it is possible to detect B7-like polypeptides through the use of a radioimmunoassay (RIA) (see, for example, Weintraub, B., Principles of Radioimmunoassays, Seventh Training Course on Radioligand Assay Techniques, The Endocrine Society, March, 1986, which is incorporated by reference herein). The radioactive isotope can be detected by means including, but not limited to, a gamma counter, a scintillation counter, or autoradiography.

[530] It is also possible to label the antibody with a fluorescent compound. When the fluorescently labeled antibody is exposed to light of the proper wave length, its presence can then be detected due to fluorescence. Among the most commonly used fluorescent labeling compounds are fluorescein isothiocyanate, rhodamine, phycoerythrin, phycocyanin, allophycocyanin, ophthaldehyde and fluorescamine.

[531] The antibody can also be detectably labeled using fluorescence emitting metals such as ^{152}Eu, or others of the lanthanide series. These metals can be attached to the antibody using such metal chelating groups as diethylenetriaminepentacetic acid (DTPA) or ethylenediaminetetraacetic acid (EDTA).

[532] The antibody also can be detectably labeled by coupling it to a chemiluminescent compound. The presence of the chemiluminescent-tagged antibody is then determined by detecting the presence of luminescence that arises during the course of a chemical reaction. Examples of particularly useful chemiluminescent labeling compounds are luminol, isoluminol, theromatic acridinium ester, imidazole, acridinium salt and oxalate ester.

[533] Likewise, a bioluminescent compound may be used to label the antibody of the

present invention. Bioluminescence is a type of chemiluminescence found in biological systems in, which a catalytic protein increases the efficiency of the chemiluminescent reaction. The presence of a bioluminescent protein is determined by detecting the presence of luminescence. Important bioluminescent compounds for purposes of labeling are luciferin, luciferase and aequorin.

Methods for Detecting Diseases

[534] In general, a disease may be detected in a patient based on the presence of one or more B7-like proteins of the invention and/or polynucleotides encoding such proteins in a biological sample (for example, blood, sera, urine, and/or tumor biopsies) obtained from the patient. In other words, such proteins may be used as markers to indicate the presence or absence of a disease or disorder, including cancer and/or as described elsewhere herein. In addition, such proteins may be useful for the detection of other diseases and cancers. The binding agents provided herein generally permit detection of the level of antigen that binds to the agent in the biological sample. Polynucleotide primers and probes may be used to detect the level of mRNA encoding B7-like polypeptides, which is also indicative of the presence or absence of a disease or disorder, including cancer. In general, B7-like polypeptides should be present at a level that is at least three fold higher in diseased tissue than in normal tissue.

[535] There are a variety of assay formats known to those of ordinary skill in the art for using a binding agent to detect polypeptide markers in a sample. See, e.g., Harlow and Lane, *supra.* In general, the presence or absence of a disease in a patient may be determined by (a) contacting a biological sample obtained from a patient with a binding agent; (b) detecting in the sample a level of polypeptide that binds to the binding agent; and (c) comparing the level of polypeptide with a predetermined cut-off value.

[536] In a preferred embodiment, the assay involves the use of a binding agent(s) immobilized on a solid support to bind to and remove the B7-like polypeptide of the invention from the remainder of the sample. The bound polypeptide may then be detected using a detection reagent that contains a reporter group and specifically binds to the binding agent/polypeptide complex. Such detection reagents may comprise, for example, a binding agent that specifically binds to the polypeptide or an antibody or other agent that specifically binds to the binding agent, such as an anti-immunoglobulin, protein G, protein A or a lectin. Alternatively, a competitive assay may be utilized, in which a polypeptide is labeled with a

reporter group and allowed to bind to the immobilized binding agent after incubation of the binding agent with the sample. The extent to which components of the sample inhibit the binding of the labeled polypeptide to the binding agent is indicative of the reactivity of the sample with the immobilized binding agent. Suitable polypeptides for use within such assays include B7-like polypeptides and portions thereof, or antibodies, to which the binding agent binds, as described above.

[537] The solid support may be any material known to those of skill in the art to which B7-like polypeptides of the invention may be attached. For example, the solid support may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane. Alternatively, the support may be a bead or disc, such as glass fiberglass, latex or a plastic material such as polystyrene or polyvinylchloride. The support may also be a magnetic particle or a fiber optic sensor, such as those disclosed, for example, in U.S. Patent No. 5,359,681. The binding agent may be immobilized on the solid support using a variety of techniques known to those of skill in the art, which are amply described in the patent and scientific literature. In the context of the present invention, the term "immobilization" refers to both noncovalent association, such as adsorption, and covalent attachment (which may be a direct linkage between the agent and functional groups on the support or may be a linkage by way of a cross-linking agent). Immobilization by adsorption to a well in a microtiter plate or to a membrane is preferred. In such cases, adsorption may be achieved by contacting the binding agent, in a suitable buffer, with the solid support for the suitable amount of time. The contact time varies with temperature, but is typically between about 1 hour and about 1 day. In general, contacting a well of plastic microtiter plate (such as polystyrene or polyvinylchloride) with an amount of binding agent ranging from about 10 ng to about 10 ug, and preferably about 100 ng to about 1 ug, is sufficient to immobilize an adequate amount of binding agent.

[538] Covalent attachment of binding agent to a solid support may generally be achieved by first reacting the support with a bifunctional reagent that will react with both the support and a functional group, such as a hydroxyl or amino group, on the binding agent. For example, the binding agent may be covalently attached to supports having an appropriate polymer coating using benzoquinone or by condensation of an aldehyde group on the support with an amine and an active hydrogen on the binding partner (see, e.g., Pierce Immunotechnology Catalog and Handbook, 1991, at A12-A13).

Gene Therapy Methods

[539] Another aspect of the present invention is to gene therapy methods for treating or preventing disorders, diseases and conditions. The gene therapy methods relate to the introduction of nucleic acid (DNA, RNA and antisense DNA or RNA) sequences into an animal to achieve expression of the polypeptide of the present invention. This method requires a polynucleotide which codes for a polypeptide of the present invention operatively linked to a promoter and any other genetic elements necessary for the expression of the polypeptide by the target tissue. Such gene therapy and delivery techniques are known in the art, see, for example, WO90/11092, which is herein incorporated by reference.

[540] Thus, for example, cells from a patient may be engineered with a polynucleotide (DNA or RNA) comprising a promoter operably linked to a polynucleotide of the present invention ex vivo, with the engineered cells then being provided to a patient to be treated with the polypeptide of the present invention. Such methods are well-known in the art. For example, see Belldegrun, A., et al., J. Natl. Cancer Inst. 85: 207-216 (1993); Ferrantini, M. et al., Cancer Research 53: 1107-1112 (1993); Ferrantini, M. et al., J. Immunology 153: 4604-4615 (1994); Kaido, T., et al., Int. J. Cancer 60: 221-229 (1995); Ogura, H., et al., Cancer Research 50: 5102-5106 (1990); Santodonato, L., et al., Human Gene Therapy 7:1-10 (1996); Santodonato, L., et al., Gene Therapy 4:1246-1255 (1997); and Zhang, J.-F. et al., Cancer Gene Therapy 3: 31-38 (1996)), which are herein incorporated by reference. In one embodiment, the cells which are engineered are arterial cells. The arterial cells may be reintroduced into the patient through direct injection to the artery, the tissues surrounding the artery, or through catheter injection.

[541] As discussed in more detail below, the polynucleotide constructs can be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, and the like). The polynucleotide constructs may be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

[542] In one embodiment, the polynucleotide of the present invention is delivered as a naked polynucleotide. The term "naked" polynucleotide, DNA or RNA refers to sequences that are free from any delivery vehicle that acts to assist, promote or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, the polynucleotide of the present invention can

also be delivered in liposome formulations and lipofectin formulations and the like can be prepared by methods well known to those skilled in the art. Such methods are described, for example, in U.S. Patent Nos. 5,593,972, 5,589,466, and 5,580,859, which are herein incorporated by reference.

[543] The polynucleotide vector constructs used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Appropriate vectors include pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; pSVK3, pBPV, pMSG and pSVL available from Pharmacia; and pEF1/V5, pcDNA3.1, and pRc/CMV2 available from Invitrogen. Other suitable vectors will be readily apparent to the skilled artisan.

[544] Any strong promoter known to those skilled in the art can be used for driving the expression of the polynucleotide sequence. Suitable promoters include adenoviral promoters, such as the adenoviral major late promoter; or heterologous promoters, such as the cytomegalovirus (CMV) promoter; the respiratory syncytial virus (RSV) promoter; inducible promoters, such as the MMT promoter, the metallothionein promoter; heat shock promoters; the albumin promoter; the ApoAI promoter; human globin promoters; viral thymidine kinase promoters, such as the Herpes Simplex thymidine kinase promoter; retroviral LTRs; the b-actin promoter; and human growth hormone promoters. The promoter also may be the native promoter for the polynucleotide of the present invention.

[545] Unlike other gene therapy techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

[546] The polynucleotide construct can be delivered to the interstitial space of tissues within the an animal, including of muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular, fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of

muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. In vivo muscle cells are particularly competent in their ability to take up and express polynucleotides.

[547] For the naked nucleic acid sequence injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 mg/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration.

[548] The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or bronchial tissues, throat or mucous membranes of the nose. In addition, naked DNA constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

[549] The naked polynucleotides are delivered by any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, and so-called "gene guns". These delivery methods are known in the art.

[550] The constructs may also be delivered with delivery vehicles such as viral sequences, viral particles, liposome formulations, lipofectin, precipitating agents, etc. Such methods of delivery are known in the art.

[551] In certain embodiments, the polynucleotide constructs are complexed in a liposome preparation. Liposomal preparations for use in the instant invention include cationic (positively charged), anionic (negatively charged) and neutral preparations. However, cationic liposomes are particularly preferred because a tight charge complex can be formed between the cationic liposome and the polyanionic nucleic acid. Cationic liposomes have been shown to mediate intracellular delivery of plasmid DNA (Felgner et al., Proc. Natl.

Acad. Sci. USA (1987) 84:7413-7416, which is herein incorporated by reference); mRNA (Malone et al., Proc. Natl. Acad. Sci. USA (1989) 86:6077-6081, which is herein incorporated by reference); and purified transcription factors (Debs et al., J. Biol. Chem. (1990) 265:10189-10192, which is herein incorporated by reference), in functional form.

[552] Cationic liposomes are readily available. For example, N[1-2,3-dioleyloxy)propyl]-N,N,N-triethylammonium (DOTMA) liposomes are particularly useful and are available under the trademark Lipofectin, from GIBCO BRL, Grand Island, N.Y. (See, also, Felgner et al., Proc. Natl Acad. Sci. USA (1987) 84:7413-7416, which is herein incorporated by reference). Other commercially available liposomes include transfectace (DDAB/DOPE) and DOTAP/DOPE (Boehringer).

[553] Other cationic liposomes can be prepared from readily available materials using techniques well known in the art. See, e.g. PCT Publication No. WO 90/11092 (which is herein incorporated by reference) for a description of the synthesis of DOTAP (1,2-bis(oleoyloxy)-3-(trimethylammonio)propane) liposomes. Preparation of DOTMA liposomes is explained in the literature, see, e.g., P. Felgner et al., Proc. Natl. Acad. Sci. USA 84:7413-7417, which is herein incorporated by reference. Similar methods can be used to prepare liposomes from other cationic lipid materials.

[554] Similarly, anionic and neutral liposomes are readily available, such as from Avanti Polar Lipids (Birmingham, Ala.), or can be easily prepared using readily available materials. Such materials include phosphatidyl, choline, cholesterol, phosphatidyl ethanolamine, dioleoylphosphatidyl choline (DOPC), dioleoylphosphatidyl glycerol (DOPG), dioleoylphoshatidyl ethanolamine (DOPE), among others. These materials can also be mixed with the DOTMA and DOTAP starting materials in appropriate ratios. Methods for making liposomes using these materials are well known in the art.

[555] For example, commercially dioleoylphosphatidyl choline (DOPC), dioleoylphosphatidyl glycerol (DOPG), and dioleoylphosphatidyl ethanolamine (DOPE) can be used in various combinations to make conventional liposomes, with or without the addition of cholesterol. Thus, for example, DOPG/DOPC vesicles can be prepared by drying 50 mg each of DOPG and DOPC under a stream of nitrogen gas into a sonication vial. The sample is placed under a vacuum pump overnight and is hydrated the following day with deionized water. The sample is then sonicated for 2 hours in a capped vial, using a Heat Systems model 350 sonicator equipped with an inverted cup (bath type) probe at the

maximum setting while the bath is circulated at 15EC. Alternatively, negatively charged vesicles can be prepared without sonication to produce multilamellar vesicles or by extrusion through nucleopore membranes to produce unilamellar vesicles of discrete size. Other methods are known and available to those of skill in the art.

[556] The liposomes can comprise multilamellar vesicles (MLVs), small unilamellar vesicles (SUVs), or large unilamellar vesicles (LUVs), with SUVs being preferred. The various liposome-nucleic acid complexes are prepared using methods well known in the art. See, e.g., Straubinger et al., Methods of Immunology (1983), 101:512-527, which is herein incorporated by reference. For example, MLVs containing nucleic acid can be prepared by depositing a thin film of phospholipid on the walls of a glass tube and subsequently hydrating with a solution of the material to be encapsulated. SUVs are prepared by extended sonication of MLVs to produce a homogeneous population of unilamellar liposomes. The material to be entrapped is added to a suspension of preformed MLVs and then sonicated. When using liposomes containing cationic lipids, the dried lipid film is resuspended in an appropriate solution such as sterile water or an isotonic buffer solution such as 10 mM Tris/NaCl, sonicated, and then the preformed liposomes are mixed directly with the DNA. The liposome and DNA form a very stable complex due to binding of the positively charged liposomes to the cationic DNA. SUVs find use with small nucleic acid fragments. LUVs are prepared by a number of methods, well known in the art. Commonly used methods include Ca^{2+}-EDTA chelation (Papahadjopoulos et al., Biochim. Biophys. Acta (1975) 394:483; Wilson et al., Cell (1979) 17:77); ether injection (Deamer, D. and Bangham, A., Biochim. Biophys. Acta (1976) 443:629; Ostro et al., Biochem. Biophys. Res. Commun. (1977) 76:836; Fraley et al., Proc. Natl. Acad. Sci. USA (1979) 76:3348); detergent dialysis (Enoch, H. and Strittmatter, P., Proc. Natl. Acad. Sci. USA (1979) 76:145); and reverse-phase evaporation (REV) (Fraley et al., J. Biol. Chem. (1980) 255:10431; Szoka, F. and Papahadjopoulos, D., Proc. Natl. Acad. Sci. USA (1978) 75:145; Schaefer-Ridder et al., Science (1982) 215:166), which are herein incorporated by reference.

[557] Generally, the ratio of DNA to liposomes will be from about 10:1 to about 1:10. Preferably, the ration will be from about 5:1 to about 1:5. More preferably, the ration will be about 3:1 to about 1:3. Still more preferably, the ratio will be about 1:1.

[558] U.S. Patent No. 5,676,954 (which is herein incorporated by reference) reports on the injection of genetic material, complexed with cationic liposomes carriers, into mice. U.S.

Patent Nos. 4,897,355, 4,946,787, 5,049,386, 5,459,127, 5,589,466, 5,693,622, 5,580,859, 5,703,055, and international publication no. WO 94/9469 (which are herein incorporated by reference) provide cationic lipids for use in transfecting DNA into cells and mammals. U.S. Patent Nos. 5,589,466, 5,693,622, 5,580,859, 5,703,055, and international publication no. WO 94/9469 (which are herein incorporated by reference) provide methods for delivering DNA-cationic lipid complexes to mammals.

[559] In certain embodiments, cells are engineered, ex vivo or in vivo, using a retroviral particle containing RNA which comprises a sequence encoding a polypeptide of the present invention. Retroviruses from which the retroviral plasmid vectors may be derived include, but are not limited to, Moloney Murine Leukemia Virus, spleen necrosis virus, Rous sarcoma Virus, Harvey Sarcoma Virus, avian leukosis virus, gibbon ape leukemia virus, human immunodeficiency virus, Myeloproliferative Sarcoma Virus, and mammary tumor virus.

[560] The retroviral plasmid vector is employed to transduce packaging cell lines to form producer cell lines. Examples of packaging cells which may be transfected include, but are not limited to, the PE501, PA317, R-2, R-AM, PA12, T19-14X, VT-19-17-H2, RCRE, RCRIP, GP+E-86, GP+envAm12, and DAN cell lines as described in Miller, Human Gene Therapy 1:5-14 (1990), which is incorporated herein by reference in its entirety. The vector may transduce the packaging cells through any means known in the art. Such means include, but are not limited to, electroporation, the use of liposomes, and $CaPO_4$ precipitation. In one alternative, the retroviral plasmid vector may be encapsulated into a liposome, or coupled to a lipid, and then administered to a host.

[561] The producer cell line generates infectious retroviral vector particles which include polynucleotide encoding a polypeptide of the present invention. Such retroviral vector particles then may be employed, to transduce eukaryotic cells, either in vitro or in vivo. The transduced eukaryotic cells will express a polypeptide of the present invention.

[562] In certain other embodiments, cells are engineered, ex vivo or in vivo, with polynucleotide contained in an adenovirus vector. Adenovirus can be manipulated such that it encodes and expresses a polypeptide of the present invention, and at the same time is inactivated in terms of its ability to replicate in a normal lytic viral life cycle. Adenovirus expression is achieved without integration of the viral DNA into the host cell chromosome, thereby alleviating concerns about insertional mutagenesis. Furthermore, adenoviruses have been used as live enteric vaccines for many years with an excellent safety profile (Schwartz,

A. R. et al. (1974) Am. Rev. Respir. Dis.109:233-238). Finally, adenovirus mediated gene transfer has been demonstrated in a number of instances including transfer of alpha-1-antitrypsin and CFTR to the lungs of cotton rats (Rosenfeld, M. A. et al. (1991) Science 252:431-434; Rosenfeld et al., (1992) Cell 68:143-155). Furthermore, extensive studies to attempt to establish adenovirus as a causative agent in human cancer were uniformly negative (Green, M. et al. (1979) Proc. Natl. Acad. Sci. USA 76:6606).

[563] Suitable adenoviral vectors useful in the present invention are described, for example, in Kozarsky and Wilson, Curr. Opin. Genet. Devel. 3:499-503 (1993); Rosenfeld et al., Cell 68:143-155 (1992); Engelhardt et al., Human Genet. Ther. 4:759-769 (1993); Yang et al., Nature Genet. 7:362-369 (1994); Wilson et al., Nature 365:691-692 (1993); and U.S. Patent No. 5,652,224, which are herein incorporated by reference. For example, the adenovirus vector Ad2 is useful and can be grown in human 293 cells. These cells contain the El region of adenovirus and constitutively express Ela and Elb, which complement the defective adenoviruses by providing the products of the genes deleted from the vector. In addition to Ad2, other varieties of adenovirus (e.g., Ad3, Ad5, and Ad7) are also useful in the present invention.

[564] Preferably, the adenoviruses used in the present invention are replication deficient. Replication deficient adenoviruses require the aid of a helper virus and/or packaging cell line to form infectious particles. The resulting virus is capable of infecting cells and can express a polynucleotide of interest which is operably linked to a promoter, but cannot replicate in most cells. Replication deficient adenoviruses may be deleted in one or more of all or a portion of the following genes: E1a, E1b, E3, E4, E2a, or L1 through L5.

[565] In certain other embodiments, the cells are engineered, ex vivo or in vivo, using an adeno-associated virus (AAV). AAVs are naturally occurring defective viruses that require helper viruses to produce infectious particles (Muzyczka, N., Curr. Topics in Microbiol. Immunol. 158:97 (1992)). It is also one of the few viruses that may integrate its DNA into non-dividing cells. Vectors containing as little as 300 base pairs of AAV can be packaged and can integrate, but space for exogenous DNA is limited to about 4.5 kb. Methods for producing and using such AAVs are known in the art. See, for example, U.S. Patent Nos. 5,139,941, 5,173,414, 5,354,678, 5,436,146, 5,474,935, 5,478,745, and 5,589,377.

[566] For example, an appropriate AAV vector for use in the present invention will include all the sequences necessary for DNA replication, encapsidation, and host-cell

integration. The polynucleotide construct is inserted into the AAV vector using standard cloning methods, such as those found in Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press (1989). The recombinant AAV vector is then transfected into packaging cells which are infected with a helper virus, using any standard technique, including lipofection, electroporation, calcium phosphate precipitation, etc. Appropriate helper viruses include adenoviruses, cytomegaloviruses, vaccinia viruses, or herpes viruses. Once the packaging cells are transfected and infected, they will produce infectious AAV viral particles which contain the polynucleotide construct. These viral particles are then used to transduce eukaryotic cells, either ex vivo or in vivo. The transduced cells will contain the polynucleotide construct integrated into its genome, and will express a polypeptide of the invention.

[567] Another method of gene therapy involves operably associating heterologous control regions and endogenous polynucleotide sequences (e.g. encoding a polypeptide of the present invention) via homologous recombination (see, e.g., U.S. Patent No. 5,641,670, issued June 24, 1997; International Publication No. WO 96/29411, published September 26, 1996; International Publication No. WO 94/12650, published August 4, 1994; Koller et al., Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); and Zijlstra et al., Nature 342:435-438 (1989). This method involves the activation of a gene which is present in the target cells, but which is not normally expressed in the cells, or is expressed at a lower level than desired.

[568] Polynucleotide constructs are made, using standard techniques known in the art, which contain the promoter with targeting sequences flanking the promoter. Suitable promoters are described herein. The targeting sequence is sufficiently complementary to an endogenous sequence to permit homologous recombination of the promoter-targeting sequence with the endogenous sequence. The targeting sequence will be sufficiently near the 5' end of the desired endogenous polynucleotide sequence so the promoter will be operably linked to the endogenous sequence upon homologous recombination.

[569] The promoter and the targeting sequences can be amplified using PCR. Preferably, the amplified promoter contains distinct restriction enzyme sites on the 5' and 3' ends. Preferably, the 3' end of the first targeting sequence contains the same restriction enzyme site as the 5' end of the amplified promoter and the 5' end of the second targeting sequence contains the same restriction site as the 3' end of the amplified promoter. The amplified promoter and targeting sequences are digested and ligated together.

[570] The promoter-targeting sequence construct is delivered to the cells, either as naked polynucleotide, or in conjunction with transfection-facilitating agents, such as liposomes, viral sequences, viral particles, whole viruses, lipofection, precipitating agents, etc., described in more detail above. The P promoter-targeting sequence can be delivered by any method, included direct needle injection, intravenous injection, topical administration, catheter infusion, particle accelerators, etc. The methods are described in more detail below.

[571] The promoter-targeting sequence construct is taken up by cells. Homologous recombination between the construct and the endogenous sequence takes place, such that an endogenous sequence is placed under the control of the promoter. The promoter then drives the expression of the endogenous sequence.

[572] Preferably, the polynucleotide encoding a polypeptide of the present invention contains a secretory signal sequence that facilitates secretion of the protein. Typically, the signal sequence is positioned in the coding region of the polynucleotide to be expressed towards or at the 5' end of the coding region. The signal sequence may be homologous or heterologous to the polynucleotide of interest and may be homologous or heterologous to the cells to be transfected. Additionally, the signal sequence may be chemically synthesized using methods known in the art.

[573] Any mode of administration of any of the above-described polynucleotides constructs can be used so long as the mode results in the expression of one or more molecules in an amount sufficient to provide a therapeutic effect. This includes direct needle injection, systemic injection, catheter infusion, biolistic injectors, particle accelerators (i.e., "gene guns"), gelfoam sponge depots, other commercially available depot materials, osmotic pumps (e.g., Alza minipumps), oral or suppositorial solid (tablet or pill) pharmaceutical formulations, and decanting or topical applications during surgery. For example, direct injection of naked calcium phosphate-precipitated plasmid into rat liver and rat spleen or a protein-coated plasmid into the portal vein has resulted in gene expression of the foreign gene in the rat livers (Kaneda et al., Science 243:375 (1989)).

[574] A preferred method of local administration is by direct injection. Preferably, a recombinant molecule of the present invention complexed with a delivery vehicle is administered by direct injection into or locally within the area of arteries. Administration of a composition locally within the area of arteries refers to injecting the composition centimeters and preferably, millimeters within arteries.

[575] Another method of local administration is to contact a polynucleotide construct of the present invention in or around a surgical wound. For example, a patient can undergo surgery and the polynucleotide construct can be coated on the surface of tissue inside the wound or the construct can be injected into areas of tissue inside the wound.

[576] Therapeutic compositions useful in systemic administration, include recombinant molecules of the present invention complexed to a targeted delivery vehicle of the present invention. Suitable delivery vehicles for use with systemic administration comprise liposomes comprising ligands for targeting the vehicle to a particular site.

[577] Preferred methods of systemic administration, include intravenous injection, aerosol, oral and percutaneous (topical) delivery. Intravenous injections can be performed using methods standard in the art. Aerosol delivery can also be performed using methods standard in the art (see, for example, Stribling et al., Proc. Natl. Acad. Sci. USA 189:11277-11281, 1992, which is incorporated herein by reference). Oral delivery can be performed by complexing a polynucleotide construct of the present invention to a carrier capable of withstanding degradation by digestive enzymes in the gut of an animal. Examples of such carriers, include plastic capsules or tablets, such as those known in the art. Topical delivery can be performed by mixing a polynucleotide construct of the present invention with a lipophilic reagent (e.g., DMSO) that is capable of passing into the skin.

[578] Determining an effective amount of substance to be delivered can depend upon a number of factors including, for example, the chemical structure and biological activity of the substance, the age and weight of the animal, the precise condition requiring treatment and its severity, and the route of administration. The frequency of treatments depends upon a number of factors, such as the amount of polynucleotide constructs administered per dose, as well as the health and history of the subject. The precise amount, number of doses, and timing of doses will be determined by the attending physician or veterinarian.

[579] Therapeutic compositions of the present invention can be administered to any animal, preferably to mammals and birds. Preferred mammals include humans, dogs, cats, mice, rats, rabbits sheep, cattle, horses and pigs, with humans being particularly preferred.

Biological Activities

[580] Polynucleotides or polypeptides, or agonists or antagonists of the present invention, can be used in assays to test for one or more biological activities. If these

polynucleotides or polypeptides, or agonists or antagonists of the present invention, do exhibit activity in a particular assay, it is likely that these molecules may be involved in the diseases associated with the biological activity. Thus, the polynucleotides and polypeptides, and agonists or antagonists could be used to treat the associated disease.

[581] Members of the B7-like family of proteins are believed to be involved in biological activities associated with T cell activation, cytokine production, T cell proliferation, and immune system and inflammatory disorders. Accordingly, compositions of the invention (including polynucleotides, polypeptides and antibodies of the invention, and fragments and variants thereof) may be used in the diagnosis, detection and/or treatment of diseases and/or disorders associated with aberrant B7-like activities.

[582] In preferred embodiments, compositions of the invention (including polynucleotides, polypeptides and antibodies of the invention, and fragments and variants thereof) may be used in the diagnosis, detection and/or treatment of diseases and/or disorders relating to the immune system in general, and T cell activation specifically (e.g., cytokine production, inflammation, T cell proliferation and T cell proliferative disorders, and/or as described under "Immune Activity", "Hyperproliferative Disorders" and "Diseases at the Cellular Level" below). Thus, polynucleotides, translation products and antibodies of the invention are useful in the diagnosis, detection and/or treatment of diseases and/or disorders associated with activities that include, but are not limited to, T cell activation, cytokine production, T cell proliferation, T cell proliferative disorders, inflammation, and immune system disorders.

[583] In certain embodiments, a polypeptide of the invention, or polynucleotides, antibodies, agonists, or antagonists corresponding to that polypeptide, may be used to diagnose and/or prognose diseases and/or disorders associated with the tissue(s) in which the polypeptide of the invention is expressed, including the tissues disclosed in "Polynucleotides and Polypeptides of the Invention", and/or one, two, three, four, five, or more tissues disclosed in Table 10, column 2 (Library Code).

[584] Thus, polynucleotides, translation products and antibodies of the invention are useful in the diagnosis, detection and/or treatment of diseases and/or disorders associated with activities that include, but are not limited to, HIV-induced dementia, arrhythmias, high blood pressure, muscular contractile dysfunction, pace-maker dysfunction, disorders of proper neurotransmitter release, epilepsy, stroke, and/or hormone secretion disorders.

[585] More generally, polynucleotides, translation products and antibodies corresponding to this gene may be useful for the diagnosis, detection and/or treatment of diseases and/or disorders associated with the following systems.

Immune Activity

[586] Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, diagnosing and/or prognosing diseases, disorders, and/or conditions of the immune system, by, for example, activating or inhibiting the proliferation, differentiation, or mobilization (chemotaxis) of immune cells. Immune cells develop through a process called hematopoiesis, producing myeloid (platelets, red blood cells, neutrophils, and macrophages) and lymphoid (B and T lymphocytes) cells from pluripotent stem cells. The etiology of these immune diseases, disorders, and/or conditions may be genetic, somatic, such as cancer and some autoimmune diseases, acquired (e.g., by chemotherapy or toxins), or infectious. Moreover, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention can be used as a marker or detector of a particular immune system disease or disorder.

[587] In another embodiment, a polypeptide of the invention, or polynucleotides, antibodies, agonists, or antagonists corresponding to that polypeptide, may be used to treat diseases and disorders of the immune system and/or to inhibit or enhance an immune response generated by cells associated with the tissue(s) in which the polypeptide of the invention is expressed, including one, two, three, four, five, or more tissues disclosed in Table 10, column 2 (Library Code).

[588] Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, diagnosing, and/or prognosing immunodeficiencies, including both congenital and acquired immunodeficiencies. Examples of B cell immunodeficiencies in which immunoglobulin levels B cell function and/or B cell numbers are decreased include: X-linked agammaglobulinemia (Bruton's disease), X-linked infantile agammaglobulinemia, X-linked immunodeficiency with hyper IgM, non X-linked immunodeficiency with hyper IgM, X-linked lymphoproliferative syndrome (XLP), agammaglobulinemia including congenital and acquired agammaglobulinemia, adult onset agammaglobulinemia, late-onset agammaglobulinemia, dysgammaglobulinemia, hypogammaglobulinemia, unspecified hypogammaglobulinemia, recessive

agammaglobulinemia (Swiss type), Selective IgM deficiency, selective IgA deficiency, selective IgG subclass deficiencies, IgG subclass deficiency (with or without IgA deficiency), Ig deficiency with increased IgM, IgG and IgA deficiency with increased IgM, antibody deficiency with normal or elevated Igs, Ig heavy chain deletions, kappa chain deficiency, B cell lymphoproliferative disorder (BLPD), common variable immunodeficiency (CVID), common variable immunodeficiency (CVI) (acquired), and transient hypogammaglobulinemia of infancy.

[589] In specific embodiments, ataxia-telangiectasia or conditions associated with ataxia-telangiectasia are treated, prevented, diagnosed, and/or prognosing using the polypeptides or polynucleotides of the invention, and/or agonists or antagonists thereof.

[590] Examples of congenital immunodeficiencies in which T cell and/or B cell function and/or number is decreased include, but are not limited to: DiGeorge anomaly, severe combined immunodeficiencies (SCID) (including, but not limited to, X-linked SCID, autosomal recessive SCID, adenosine deaminase deficiency, purine nucleoside phosphorylase (PNP) deficiency, Class II MHC deficiency (Bare lymphocyte syndrome), Wiskott-Aldrich syndrome, and ataxia telangiectasia), thymic hypoplasia, third and fourth pharyngeal pouch syndrome, 22q11.2 deletion, chronic mucocutaneous candidiasis, natural killer cell deficiency (NK), idiopathic CD4+ T-lymphocytopenia, immunodeficiency with predominant T cell defect (unspecified), and unspecified immunodeficiency of cell mediated immunity.

[591] In specific embodiments, DiGeorge anomaly or conditions associated with DiGeorge anomaly are treated, prevented, diagnosed, and/or prognosed using polypeptides or polynucleotides of the invention, or antagonists or agonists thereof.

[592] Other immunodeficiencies that may be treated, prevented, diagnosed, and/or prognosed using polypeptides or polynucleotides of the invention, and/or agonists or antagonists thereof, include, but are not limited to, chronic granulomatous disease, Chédiak-Higashi syndrome, myeloperoxidase deficiency, leukocyte glucose-6-phosphate dehydrogenase deficiency, X-linked lymphoproliferative syndrome (XLP), leukocyte adhesion deficiency, complement component deficiencies (including C1, C2, C3, C4, C5, C6, C7, C8 and/or C9 deficiencies), reticular dysgenesis, thymic alymphoplasia-aplasia, immunodeficiency with thymoma, severe congenital leukopenia, dysplasia with immunodeficiency, neonatal neutropenia, short limbed dwarfism, and Nezelof syndrome-combined immunodeficiency with Igs.

[593] In a preferred embodiment, the immunodeficiencies and/or conditions associated with the immunodeficiencies recited above are treated, prevented, diagnosed and/or prognosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention.

[594] In a preferred embodiment polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention could be used as an agent to boost immunoresponsiveness among immunodeficient individuals. In specific embodiments, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention could be used as an agent to boost immunoresponsiveness among B cell and/or T cell immunodeficient individuals.

[595] The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, diagnosing and/or prognosing autoimmune disorders. Many autoimmune disorders result from inappropriate recognition of self as foreign material by immune cells. This inappropriate recognition results in an immune response leading to the destruction of the host tissue. Therefore, the administration of polynucleotides and polypeptides of the invention that can inhibit an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing autoimmune disorders.

[596] Autoimmune diseases or disorders that may be treated, prevented, diagnosed and/or prognosed by polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention include, but are not limited to, one or more of the following: systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis, multiple sclerosis, autoimmune thyroiditis, Hashimoto's thyroiditis, autoimmune hemolytic anemia, hemolytic anemia, thrombocytopenia, autoimmune thrombocytopenia purpura, autoimmune neonatal thrombocytopenia, idiopathic thrombocytopenia purpura, purpura (e.g., Henloch-Scoenlein purpura), autoimmunocytopenia, Goodpasture's syndrome, Pemphigus vulgaris, myasthenia gravis, Grave's disease (hyperthyroidism), and insulin-resistant diabetes mellitus.

[597] Additional disorders that are likely to have an autoimmune component that may be treated, prevented, and/or diagnosed with the compositions of the invention include, but are not limited to, type II collagen-induced arthritis, antiphospholipid syndrome, dermatitis, allergic encephalomyelitis, myocarditis, relapsing polychondritis, rheumatic heart disease, neuritis, uveitis ophthalmia, polyendocrinopathies, Reiter's Disease, Stiff-Man Syndrome,

autoimmune pulmonary inflammation, autism, Guillain-Barre Syndrome, insulin dependent diabetes mellitus, and autoimmune inflammatory eye disorders.

[598] Additional disorders that are likely to have an autoimmune component that may be treated, prevented, diagnosed and/or prognosed with the compositions of the invention include, but are not limited to, scleroderma with anti-collagen antibodies (often characterized, e.g., by nucleolar and other nuclear antibodies), mixed connective tissue disease (often characterized, e.g., by antibodies to extractable nuclear antigens (e.g., ribonucleoprotein)), polymyositis (often characterized, e.g., by nonhistone ANA), pernicious anemia (often characterized, e.g., by antiparietal cell, microsomes, and intrinsic factor antibodies), idiopathic Addison's disease (often characterized, e.g., by humoral and cell-mediated adrenal cytotoxicity, infertility (often characterized, e.g., by antispermatozoal antibodies), glomerulonephritis (often characterized, e.g., by glomerular basement membrane antibodies or immune complexes), bullous pemphigoid (often characterized, e.g., by IgG and complement in basement membrane), Sjogren's syndrome (often characterized, e.g., by multiple tissue antibodies, and/or a specific nonhistone ANA (SS-B)), diabetes mellitus (often characterized, e.g., by cell-mediated and humoral islet cell antibodies), and adrenergic drug resistance (including adrenergic drug resistance with asthma or cystic fibrosis) (often characterized, e.g., by beta-adrenergic receptor antibodies).

[599] Additional disorders that may have an autoimmune component that may be treated, prevented, diagnosed and/or prognosed with the compositions of the invention include, but are not limited to, chronic active hepatitis (often characterized, e.g., by smooth muscle antibodies), primary biliary cirrhosis (often characterized, e.g., by mitochondria antibodies), other endocrine gland failure (often characterized, e.g., by specific tissue antibodies in some cases), vitiligo (often characterized, e.g., by melanocyte antibodies), vasculitis (often characterized, e.g., by Ig and complement in vessel walls and/or low serum complement), post-MI (often characterized, e.g., by myocardial antibodies), cardiotomy syndrome (often characterized, e.g., by myocardial antibodies), urticaria (often characterized, e.g., by IgG and IgM antibodies to IgE), atopic dermatitis (often characterized, e.g., by IgG and IgM antibodies to IgE), asthma (often characterized, e.g., by IgG and IgM antibodies to IgE), and many other inflammatory, granulomatous, degenerative, and atrophic disorders.

[600] In a preferred embodiment, the autoimmune diseases and disorders and/or conditions associated with the diseases and disorders recited above are treated, prevented,

diagnosed and/or prognosed using for example, antagonists or agonists, polypeptides or polynucleotides, or antibodies of the present invention. In a specific preferred embodiment, rheumatoid arthritis is treated, prevented, and/or diagnosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention.

[601] In another specific preferred embodiment, systemic lupus erythematosus is treated, prevented, and/or diagnosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention. In another specific preferred embodiment, idiopathic thrombocytopenia purpura is treated, prevented, and/or diagnosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention.

[602] In another specific preferred embodiment IgA nephropathy is treated, prevented, and/or diagnosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention.

[603] In a preferred embodiment, the autoimmune diseases and disorders and/or conditions associated with the diseases and disorders recited above are treated, prevented, diagnosed and/or prognosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention

[604] In preferred embodiments, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a immunosuppressive agent(s).

[605] Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, prognosing, and/or diagnosing diseases, disorders, and/or conditions of hematopoietic cells. Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention could be used to increase differentiation and proliferation of hematopoietic cells, including the pluripotent stem cells, in an effort to treat or prevent those diseases, disorders, and/or conditions associated with a decrease in certain (or many) types hematopoietic cells, including but not limited to, leukopenia, neutropenia, anemia, and thrombocytopenia. Alternatively, Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention could be used to increase differentiation and proliferation of hematopoietic cells, including the pluripotent stem cells, in an effort to treat or prevent those diseases, disorders, and/or conditions associated with an increase in certain (or many) types of hematopoietic cells, including but not limited to, histiocytosis.

[606] Allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems, may also be treated, prevented, diagnosed and/or prognosed using polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof. Moreover, these molecules can be used to treat, prevent, prognose, and/or diagnose anaphylaxis, hypersensitivity to an antigenic molecule, or blood group incompatibility.

[607] Additionally, polypeptides or polynucleotides of the invention, and/or agonists or antagonists thereof, may be used to treat, prevent, diagnose and/or prognose IgE-mediated allergic reactions. Such allergic reactions include, but are not limited to, asthma, rhinitis, and eczema. In specific embodiments, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to modulate IgE concentrations in vitro or in vivo.

[608] Moreover, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention have uses in the diagnosis, prognosis, prevention, and/or treatment of inflammatory conditions. For example, since polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists of the invention may inhibit the activation, proliferation and/or differentiation of cells involved in an inflammatory response, these molecules can be used to prevent and/or treat chronic and acute inflammatory conditions. Such inflammatory conditions include, but are not limited to, for example, inflammation associated with infection (e.g., septic shock, sepsis, or systemic inflammatory response syndrome), ischemia-reperfusion injury, endotoxin lethality, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine induced lung injury, inflammatory bowel disease, Crohn's disease, over production of cytokines (e.g., TNF or IL-1.), respiratory disorders (e.g., asthma and allergy); gastrointestinal disorders (e.g., inflammatory bowel disease); cancers (e.g., gastric, ovarian, lung, bladder, liver, and breast); CNS disorders (e.g., multiple sclerosis; ischemic brain injury and/or stroke, traumatic brain injury, neurodegenerative disorders (e.g., Parkinson's disease and Alzheimer's disease); AIDS-related dementia; and prion disease); cardiovascular disorders (e.g., atherosclerosis, myocarditis, cardiovascular disease, and cardiopulmonary bypass complications); as well as many additional diseases, conditions, and disorders that are characterized by inflammation (e.g., hepatitis, rheumatoid arthritis, gout, trauma, pancreatitis, sarcoidosis, dermatitis, renal ischemia-reperfusion injury, Grave's disease, systemic lupus erythematosus, diabetes mellitus, and allogenic transplant rejection).

[609] Because inflammation is a fundamental defense mechanism, inflammatory disorders can effect virtually any tissue of the body. Accordingly, polynucleotides, polypeptides, and antibodies of the invention, as well as agonists or antagonists thereof, have uses in the treatment of tissue-specific inflammatory disorders, including, but not limited to, adrenalitis, alveolitis, angiocholecystitis, appendicitis, balanitis, blepharitis, bronchitis, bursitis, carditis, cellulitis, cervicitis, cholecystitis, chorditis, cochlitis, colitis, conjunctivitis, cystitis, dermatitis, diverticulitis, encephalitis, endocarditis, esophagitis, eustachitis, fibrositis, folliculitis, gastritis, gastroenteritis, gingivitis, glossitis, hepatosplenitis, keratitis, labyrinthitis, laryngitis, lymphangitis, mastitis, media otitis, meningitis, metritis, mucitis, myocarditis, myosititis, myringitis, nephritis, neuritis, orchitis, osteochondritis, otitis, pericarditis, peritendonitis, peritonitis, pharyngitis, phlebitis, poliomyelitis, prostatitis, pulpitis, retinitis, rhinitis, salpingitis, scleritis, sclerochoroiditis, scrotitis, sinusitis, spondylitis, steatitis, stomatitis, synovitis, syringitis, tendonitis, tonsillitis, urethritis, and vaginitis.

[610] In specific embodiments, polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof, are useful to diagnose, prognose, prevent, and/or treat organ transplant rejections and graft-versus-host disease. Organ rejection occurs by host immune cell destruction of the transplanted tissue through an immune response. Similarly, an immune response is also involved in GVHD, but, in this case, the foreign transplanted immune cells destroy the host tissues. Polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof, that inhibit an immune response, particularly the activation, proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing organ rejection or GVHD. In specific embodiments, polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof, that inhibit an immune response, particularly the activation, proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing experimental allergic and hyperacute xenograft rejection.

[611] In other embodiments, polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof, are useful to diagnose, prognose, prevent, and/or treat immune complex diseases, including, but not limited to, serum sickness, post streptococcal glomerulonephritis, polyarteritis nodosa, and immune complex-induced vasculitis.

[612] Polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the invention can be used to treat, detect, and/or prevent infectious agents. For example, by increasing the immune response, particularly increasing the proliferation activation and/or differentiation of B and/or T cells, infectious diseases may be treated, detected, and/or prevented. The immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may also directly inhibit the infectious agent (refer to section of application listing infectious agents, etc), without necessarily eliciting an immune response.

[613] In another embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a vaccine adjuvant that enhances immune responsiveness to an antigen. In a specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an adjuvant to enhance tumor-specific immune responses.

[614] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an adjuvant to enhance anti-viral immune responses. Anti-viral immune responses that may be enhanced using the compositions of the invention as an adjuvant, include virus and virus associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a virus, disease, or symptom selected from the group consisting of: AIDS, meningitis, Dengue, EBV, and hepatitis (e.g., hepatitis B). In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to a virus, disease, or symptom selected from the group consisting of: HIV/AIDS, respiratory syncytial virus, Dengue, rotavirus, Japanese B encephalitis, influenza A and B, parainfluenza, measles, cytomegalovirus, rabies, Junin, Chikungunya, Rift Valley Fever, herpes simplex, and yellow fever.

[615] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an adjuvant to enhance anti-bacterial or anti-fungal immune responses. Anti-bacterial or anti-fungal immune responses that may be enhanced using the compositions of the invention as an adjuvant, include bacteria or fungus and bacteria or fungus associated diseases or symptoms described herein or

otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a bacteria or fungus, disease, or symptom selected from the group consisting of: tetanus, Diphtheria, botulism, and meningitis type B.

[616] In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to a bacteria or fungus, disease, or symptom selected from the group consisting of: *Vibrio cholerae, Mycobacterium leprae, Salmonella typhi, Salmonella paratyphi, Meisseria meningitidis, Streptococcus pneumoniae,* Group B streptococcus, *Shigella spp.*, Enterotoxigenic *Escherichia coli,* Enterohemorrhagic *E. coli*, and *Borrelia burgdorferi*.

[617] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an adjuvant to enhance anti-parasitic immune responses. Anti-parasitic immune responses that may be enhanced using the compositions of the invention as an adjuvant, include parasite and parasite associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a parasite. In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to Plasmodium (malaria) or Leishmania.

[618] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may also be employed to treat infectious diseases including silicosis, sarcoidosis, and idiopathic pulmonary fibrosis; for example, by preventing the recruitment and activation of mononuclear phagocytes.

[619] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an antigen for the generation of antibodies to inhibit or enhance immune mediated responses against polypeptides of the invention.

[620] In one embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are administered to an animal (e.g., mouse, rat, rabbit, hamster, guinea pig, pigs, micro-pig, chicken, camel, goat, horse, cow, sheep, dog, cat, non-human primate, and human, most preferably human) to boost the immune system to produce increased quantities of one or more antibodies (e.g., IgG, IgA, IgM, and IgE), to induce

higher affinity antibody production and immunoglobulin class switching (e.g., IgG, IgA, IgM, and IgE), and/or to increase an immune response.

[621] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a stimulator of B cell responsiveness to pathogens.

[622] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an activator of T cells.

[623] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent that elevates the immune status of an individual prior to their receipt of immunosuppressive therapies.

[624] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to induce higher affinity antibodies.

[625] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to increase serum immunoglobulin concentrations.

[626] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to accelerate recovery of immunocompromised individuals.

[627] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to boost immunoresponsiveness among aged populations and/or neonates.

[628] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an immune system enhancer prior to, during, or after bone marrow transplant and/or other transplants (e.g., allogeneic or xenogeneic organ transplantation). With respect to transplantation, compositions of the invention may be administered prior to, concomitant with, and/or after transplantation. In a specific embodiment, compositions of the invention are administered after transplantation, prior to the beginning of recovery of T-cell populations. In another specific embodiment, compositions of the invention are first administered after transplantation after the beginning of recovery of T cell populations, but prior to full recovery of B cell populations.

[629] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to boost immunoresponsiveness among individuals having an acquired loss of B cell function. Conditions resulting in an acquired loss of B cell function that may be ameliorated or treated by administering the polypeptides, antibodies, polynucleotides and/or agonists or antagonists thereof, include, but are not limited to, HIV Infection, AIDS, bone marrow transplant, and B cell chronic lymphocytic leukemia (CLL).

[630] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to boost immunoresponsiveness among individuals having a temporary immune deficiency. Conditions resulting in a temporary immune deficiency that may be ameliorated or treated by administering the polypeptides, antibodies, polynucleotides and/or agonists or antagonists thereof, include, but are not limited to, recovery from viral infections (e.g., influenza), conditions associated with malnutrition, recovery from infectious mononucleosis, or conditions associated with stress, recovery from measles, recovery from blood transfusion, and recovery from surgery.

[631] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a regulator of antigen presentation by monocytes, dendritic cells, and/or B-cells. In one embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention enhance antigen presentation or antagonizes antigen presentation in vitro or in vivo. Moreover, in related embodiments, said enhancement or antagonism of antigen presentation may be useful as an anti-tumor treatment or to modulate the immune system.

[632] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to direct an individual's immune system towards development of a humoral response (i.e. TH2) as opposed to a TH1 cellular response.

[633] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a means to induce tumor proliferation and thus make it more susceptible to anti-neoplastic agents. For example, multiple myeloma is a slowly dividing disease and is thus refractory to virtually all anti-

neoplastic regimens. If these cells were forced to proliferate more rapidly their susceptibility profile would likely change.

[634] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a stimulator of B cell production in pathologies such as AIDS, chronic lymphocyte disorder and/or Common Variable Immunodificiency.

[635] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a therapy for generation and/or regeneration of lymphoid tissues following surgery, trauma or genetic defect. In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used in the pretreatment of bone marrow samples prior to transplant.

[636] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a gene-based therapy for genetically inherited disorders resulting in immuno-incompetence/immunodeficiency such as observed among SCID patients.

[637] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a means of activating monocytes/macrophages to defend against parasitic diseases that effect monocytes such as Leishmania.

[638] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a means of regulating secreted cytokines that are elicited by polypeptides of the invention.

[639] In another embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used in one or more of the applications decribed herein, as they may apply to veterinary medicine.

[640] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a means of blocking various aspects of immune responses to foreign agents or self. Examples of diseases or conditions in which blocking of certain aspects of immune responses may be desired include autoimmune disorders such as lupus, and arthritis, as well as immunoresponsiveness to skin allergies, inflammation, bowel disease, injury and diseases/disorders associated with pathogens.

[641] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a therapy for preventing the B cell proliferation and Ig secretion associated with autoimmune diseases such as idiopathic thrombocytopenic purpura, systemic lupus erythematosus and multiple sclerosis.

[642] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a inhibitor of B and/or T cell migration in endothelial cells. This activity disrupts tissue architecture or cognate responses and is useful, for example in disrupting immune responses, and blocking sepsis.

[643] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a therapy for chronic hypergammaglobulinemia evident in such diseases as monoclonal gammopathy of undetermined significance (MGUS), Waldenstrom's disease, related idiopathic monoclonal gammopathies, and plasmacytomas.

[644] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may be employed for instance to inhibit polypeptide chemotaxis and activation of macrophages and their precursors, and of neutrophils, basophils, B lymphocytes and some T-cell subsets, e.g., activated and CD8 cytotoxic T cells and natural killer cells, in certain autoimmune and chronic inflammatory and infective diseases. Examples of autoimmune diseases are described herein and include multiple sclerosis, and insulin-dependent diabetes.

[645] The polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may also be employed to treat idiopathic hyper-eosinophilic syndrome by, for example, preventing eosinophil production and migration.

[646] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used to enhance or inhibit complement mediated cell lysis.

[647] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used to enhance or inhibit antibody dependent cellular cytotoxicity.

[648] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may also be employed for treating atherosclerosis, for example, by preventing monocyte infiltration in the artery wall.

[649] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may be employed to treat adult respiratory distress syndrome (ARDS).

[650] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may be useful for stimulating wound and tissue repair, stimulating angiogenesis, and/or stimulating the repair of vascular or lymphatic diseases or disorders. Additionally, agonists and antagonists of the invention may be used to stimulate the regeneration of mucosal surfaces.

[651] In a specific embodiment, polynucleotides or polypeptides, and/or agonists thereof are used to diagnose, prognose, treat, and/or prevent a disorder characterized by primary or acquired immunodeficiency, deficient serum immunoglobulin production, recurrent infections, and/or immune system dysfunction. Moreover, polynucleotides or polypeptides, and/or agonists thereof may be used to treat or prevent infections of the joints, bones, skin, and/or parotid glands, blood-borne infections (e.g., sepsis, meningitis, septic arthritis, and/or osteomyelitis), autoimmune diseases (e.g., those disclosed herein), inflammatory disorders, and malignancies, and/or any disease or disorder or condition associated with these infections, diseases, disorders and/or malignancies) including, but not limited to, CVID, other primary immune deficiencies, HIV disease, CLL, recurrent bronchitis, sinusitis, otitis media, conjunctivitis, pneumonia, hepatitis, meningitis, herpes zoster (e.g., severe herpes zoster), and/or pneumocystis carnii. Other diseases and disorders that may be prevented, diagnosed, prognosed, and/or treated with polynucleotides or polypeptides, and/or agonists of the present invention include, but are not limited to, HIV infection, HTLV-BLV infection, lymphopenia, phagocyte bactericidal dysfunction anemia, thrombocytopenia, and hemoglobinuria.

[652] In another embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention are used to treat, and/or diagnose an individual having common variable immunodeficiency disease ("CVID"; also known as "acquired agammaglobulinemia" and "acquired hypogammaglobulinemia") or a subset of this disease.

[653] In a specific embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to diagnose, prognose, prevent, and/or treat cancers or neoplasms including immune cell or immune tissue-related cancers or neoplasms. Examples of cancers or neoplasms that may be prevented, diagnosed, or treated by polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present

invention include, but are not limited to, acute myelogenous leukemia, chronic myelogenous leukemia, Hodgkin's disease, non-Hodgkin's lymphoma, acute lymphocytic anemia (ALL) Chronic lymphocyte leukemia, plasmacytomas, multiple myeloma, Burkitt's lymphoma, EBV-transformed diseases, and/or diseases and disorders described in the section entitled "Hyperproliferative Disorders" elsewhere herein.

[654] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a therapy for decreasing cellular proliferation of Large B-cell Lymphomas.

[655] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a means of decreasing the involvement of B cells and Ig associated with Chronic Myelogenous Leukemia.

[656] In specific embodiments, the compositions of the invention are used as an agent to boost immunoresponsiveness among B cell immunodeficient individuals, such as, for example, an individual who has undergone a partial or complete splenectomy.

[657] Antagonists of the invention include, for example, binding and/or inhibitory antibodies, antisense nucleic acids, ribozymes or soluble forms of the polypeptides of the present invention (e.g., Fc fusion protein; see,. e.g., Example 9). Agonists of the invention include, for example, binding or stimulatory antibodies, and soluble forms of the polypeptides (e.g., Fc fusion proteins; see, e.g., Example 9). polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may be employed in a composition with a pharmaceutically acceptable carrier, e.g., as described herein.

[658] In another embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are administered to an animal (including, but not limited to, those listed above, and also including transgenic animals) incapable of producing functional endogenous antibody molecules or having an otherwise compromised endogenous immune system, but which is capable of producing human immunoglobulin molecules by means of a reconstituted or partially reconstituted immune system from another animal (see, e.g., published PCT Application Nos. WO98/24893, WO/9634096, WO/9633735, and WO/9110741). Administration of polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention to such animals is useful for the generation of monoclonal antibodies against the polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention.

Blood-Related Disorders

[659] The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to modulate hemostatic (the stopping of bleeding) or thrombolytic (clot dissolving) activity. For example, by increasing hemostatic or thrombolytic activity, polynucleotides or polypeptides, and/or agonists or antagonists of the present invention could be used to treat or prevent blood coagulation diseases, disorders, and/or conditions (e.g., afibrinogenemia, factor deficiencies, hemophilia), blood platelet diseases, disorders, and/or conditions (e.g., thrombocytopenia), or wounds resulting from trauma, surgery, or other causes. Alternatively, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention that can decrease hemostatic or thrombolytic activity could be used to inhibit or dissolve clotting. These molecules could be important in the treatment or prevention of heart attacks (infarction), strokes, or scarring.

[660] In specific embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to prevent, diagnose, prognose, and/or treat thrombosis, arterial thrombosis, venous thrombosis, thromboembolism, pulmonary embolism, atherosclerosis, myocardial infarction, transient ischemic attack, unstable angina. In specific embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used for the prevention of occulsion of saphenous grafts, for reducing the risk of periprocedural thrombosis as might accompany angioplasty procedures, for reducing the risk of stroke in patients with atrial fibrillation including nonrheumatic atrial fibrillation, for reducing the risk of embolism associated with mechanical heart valves and or mitral valves disease. Other uses for the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention, include, but are not limited to, the prevention of occlusions in extrcorporeal devices (e.g., intravascular canulas, vascular access shunts in hemodialysis patients, hemodialysis machines, and cardiopulmonary bypass machines).

[661] In another embodiment, a polypeptide of the invention, or polynucleotides, antibodies, agonists, or antagonists corresponding to that polypeptide, may be used to prevent, diagnose, prognose, and/or treat diseases and disorders of the blood and/or blood forming organs associated with the tissue(s) in which the polypeptide of the invention is

expressed, including one, two, three, four, five, or more tissues disclosed in Table 10, column 2 (Library Code).

[662] The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to modulate hematopoietic activity (the formation of blood cells). For example, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to increase the quantity of all or subsets of blood cells, such as, for example, erythrocytes, lymphocytes (B or T cells), myeloid cells (e.g., basophils, eosinophils, neutrophils, mast cells, macrophages) and platelets. The ability to decrease the quantity of blood cells or subsets of blood cells may be useful in the prevention, detection, diagnosis and/or treatment of anemias and leukopenias described below. Alternatively, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to decrease the quantity of all or subsets of blood cells, such as, for example, erythrocytes, lymphocytes (B or T cells), myeloid cells (e.g., basophils, eosinophils, neutrophils, mast cells, macrophages) and platelets.. The ability to decrease the quantity of blood cells or subsets of blood cells may be useful in the prevention, detection, diagnosis and/or treatment of leukocytoses, such as, for example eosinophilia.

[663] The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to prevent, treat, or diagnose blood dyscrasia.

[664] Anemias are conditions in which the number of red blood cells or amount of hemoglobin (the protein that carries oxygen) in them is below normal. Anemia may be caused by excessive bleeding, decreased red blood cell production, or increased red blood cell destruction (hemolysis). The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing anemias. Anemias that may be treated prevented or diagnosed by the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention include iron deficiency anemia, hypochromic anemia, microcytic anemia, chlorosis, hereditary siderob;astic anemia, idiopathic acquired sideroblastic anemia, red cell aplasia, megaloblastic anemia (e.g., pernicious anemia, (vitamin B12 deficiency) and folic acid deficiency anemia), aplastic anemia, hemolytic anemias (e.g., autoimmune helolytic anemia, microangiopathic hemolytic anemia, and paroxysmal nocturnal hemoglobinuria). The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present

invention may be useful in treating, preventing, and/or diagnosing anemias associated with diseases including but not limited to, anemias associated with systemic lupus erythematosus, cancers, lymphomas, chronic renal disease, and enlarged spleens. The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing anemias arising from drug treatments such as anemias associated with methyldopa, dapsone, and/or sulfadrugs. Additionally, rhe polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing anemias associated with abnormal red blood cell architecture including but not limited to, hereditary spherocytosis, hereditary elliptocytosis, glucose-6-phosphate dehydrogenase deficiency, and sickle cell anemia.

[665] The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing hemoglobin abnormalities, (e.g., those associated with sickle cell anemia, hemoglobin C disease, hemoglobin S-C disease, and hemoglobin E disease). Additionally, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating thalassemias, including, but not limited to major and minor forms of alpha-thalassemia and beta-thalassemia.

[666] In another embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating bleeding disorders including, but not limited to, thrombocytopenia (e.g., idiopathic thrombocytopenic purpura, and thrombotic thrombocytopenic purpura), Von Willebrand's disease, hereditary platelet disorders (e.g., storage pool disease such as Chediak-Higashi and Hermansky-Pudlak syndromes, thromboxane A2 dysfunction, thromboasthenia, and Bernard-Soulier syndrome), hemolytic-uremic syndrome, hemophelias such as hemophelia A or Factor VII deficiency and Christmas disease or Factor IX deficiency, Hereditary Hemorhhagic Telangiectsia, also known as Rendu-Osler-Weber syndrome, allergic purpura (Henoch Schonlein purpura) and disseminated intravascular coagulation.

[667] The effect of the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention on the clotting time of blood may be monitored using any of the clotting tests known in the art including, but not limited to, whole blood partial

thromboplastin time (PTT), the activated partial thromboplastin time (aPTT), the activated clotting time (ACT), the recalcified activated clotting time, or the Lee-White Clotting time.

[668] Several diseases and a variety of drugs can cause platelet dysfunction. Thus, in a specific embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating acquired platelet dysfunction such as platelet dysfunction accompanying kidney failure, leukemia, multiple myeloma, cirrhosis of the liver, and systemic lupus erythematosus as well as platelet dysfunction associated with drug treatments, including treatment with aspirin, ticlopidine, nonsteroidal anti-inflammatory drugs (used for arthritis, pain, and sprains), and penicillin in high doses.

[669] In another embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating diseases and disorders characterized by or associated with increased or decreased numbers of white blood cells. Leukopenia occurs when the number of white blood cells decreases below normal. Leukopenias include, but are not limited to, neutropenia and lymphocytopenia. An increase in the number of white blood cells compared to normal is known as leukocytosis. The body generates increased numbers of white blood cells during infection. Thus, leukocytosis may simply be a normal physiological parameter that reflects infection. Alternatively, leukocytosis may be an indicator of injury or other disease such as cancer. Leokocytoses, include but are not limited to, eosinophilia, and accumulations of macrophages. In specific embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating leukopenia. In other specific embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating leukocytosis.

[670] Leukopenia may be a generalized decreased in all types of white blood cells, or may be a specific depletion of particular types of white blood cells. Thus, in specific embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating decreases in neutrophil numbers, known as neutropenia. Neutropenias that may be diagnosed, prognosed, prevented, and/or treated by the polynucleotides, polypeptides,

antibodies, and/or agonists or antagonists of the present invention include, but are not limited to, infantile genetic agranulocytosis, familial neutropenia, cyclic neutropenia, neutropenias resulting from or associated with dietary deficiencies (e.g., vitamin B 12 deficiency or folic acid deficiency), neutropenias resulting from or associated with drug treatments (e.g., antibiotic regimens such as penicillin treatment, sulfonamide treatment, anticoagulant treatment, anticonvulsant drugs, anti-thyroid drugs, and cancer chemotherapy), and neutropenias resulting from increased neutrophil destruction that may occur in association with some bacterial or viral infections, allergic disorders, autoimmune diseases, conditions in which an individual has an enlarged spleen (e.g., Felty syndrome, malaria and sarcoidosis), and some drug treatment regimens.

[671] The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating lymphocytopenias (decreased numbers of B and/or T lymphocytes), including, but not limited lymphocytopenias resulting from or associated with stress, drug treatments (e.g., drug treatment with corticosteroids, cancer chemotherapies, and/or radiation therapies), AIDS infection and/or other diseases such as, for example, cancer, rheumatoid arthritis, systemic lupus erythematosus, chronic infections, some viral infections and/or hereditary disorders (e.g., DiGeorge syndrome, Wiskott-Aldrich Syndome, severe combined immunodeficiency, ataxia telangiectsia).

[672] The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating diseases and disorders associated with macrophage numbers and/or macrophage function including, but not limited to, Gaucher's disease, Niemann-Pick disease, Letterer-Siwe disease and Hand-Schuller-Christian disease.

[673] In another embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating diseases and disorders associated with eosinophil numbers and/or eosinophil function including, but not limited to, idiopathic hypereosinophilic syndrome, eosinophilia-myalgia syndrome, and Hand-Schuller-Christian disease.

[674] In yet another embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating leukemias and lymphomas including, but not limited to, acute

lymphocytic (lymphpblastic) leukemia (ALL), acute myeloid (myelocytic, myelogenous, myeloblastic, or myelomonocytic) leukemia, chronic lymphocytic leukemia (e.g., B cell leukemias, T cell leukemias, Sezary syndrome, and Hairy cell leukenia), chronic myelocytic (myeloid, myelogenous, or granulocytic) leukemia, Hodgkin's lymphoma, non-hodgkin's lymphoma, Burkitt's lymphoma, and mycosis fungoides.

[675] In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating diseases and disorders of plasma cells including, but not limited to, plasma cell dyscrasias, monoclonal gammaopathies, monoclonal gammopathies of undetermined significance, multiple myeloma, macroglobulinemia, Waldenstrom's macroglobulinemia, cryoglobulinemia, and Raynaud's phenomenon.

[676] In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing myeloproliferative disorders, including but not limited to, polycythemia vera, relative polycythemia, secondary polycythemia, myelofibrosis, acute myelofibrosis, agnogenic myelod metaplasia, thrombocythemia, (including both primary and seconday thrombocythemia) and chronic myelocytic leukemia.

[677] In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful as a treatment prior to surgery, to increase blood cell production.

[678] In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful as an agent to enhance the migration, phagocytosis, superoxide production, antibody dependent cellular cytotoxicity of neutrophils, eosionophils and macrophages.

[679] In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful as an agent to increase the number of stem cells in circulation prior to stem cells pheresis. In another specific embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful as an agent to increase the number of stem cells in circulation prior to platelet pheresis.

[680] In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful as an agent to increase cytokine production.

[681] In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in preventing, diagnosing, and/or treating primary hematopoietic disorders.

Hyperproliferative Disorders

[682] In certain embodiments, polynucleotides or polypeptides, or agonists or antagonists of the present invention can be used to treat or detect hyperproliferative disorders, including neoplasms. Polynucleotides or polypeptides, or agonists or antagonists of the present invention may inhibit the proliferation of the disorder through direct or indirect interactions. Alternatively, Polynucleotides or polypeptides, or agonists or antagonists of the present invention may proliferate other cells which can inhibit the hyperproliferative disorder.

[683] For example, by increasing an immune response, particularly increasing antigenic qualities of the hyperproliferative disorder or by proliferating, differentiating, or mobilizing T-cells, hyperproliferative disorders can be treated. This immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, decreasing an immune response may also be a method of treating hyperproliferative disorders, such as a chemotherapeutic agent.

[684] Examples of hyperproliferative disorders that can be treated or detected by polynucleotides or polypeptides, or agonists or antagonists of the present invention include, but are not limited to neoplasms located in the: colon, abdomen, bone, breast, digestive system, liver, pancreas, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous (central and peripheral), lymphatic system, pelvis, skin, soft tissue, spleen, thorax, and urogenital tract.

[685] Similarly, other hyperproliferative disorders can also be treated or detected by polynucleotides or polypeptides, or agonists or antagonists of the present invention. Examples of such hyperproliferative disorders include, but are not limited to: Acute Childhood Lymphoblastic Leukemia, Acute Lymphoblastic Leukemia, Acute Lymphocytic Leukemia, Acute Myeloid Leukemia, Adrenocortical Carcinoma, Adult (Primary)

Hepatocellular Cancer, Adult (Primary) Liver Cancer, Adult Acute Lymphocytic Leukemia, Adult Acute Myeloid Leukemia, Adult Hodgkin's Disease, Adult Hodgkin's Lymphoma, Adult Lymphocytic Leukemia, Adult Non-Hodgkin's Lymphoma, Adult Primary Liver Cancer, Adult Soft Tissue Sarcoma, AIDS-Related Lymphoma, AIDS-Related Malignancies, Anal Cancer, Astrocytoma, Bile Duct Cancer, Bladder Cancer, Bone Cancer, Brain Stem Glioma, Brain Tumors, Breast Cancer, Cancer of the Renal Pelvis and Ureter, Central Nervous System (Primary) Lymphoma, Central Nervous System Lymphoma, Cerebellar Astrocytoma, Cerebral Astrocytoma, Cervical Cancer, Childhood (Primary) Hepatocellular Cancer, Childhood (Primary) Liver Cancer, Childhood Acute Lymphoblastic Leukemia, Childhood Acute Myeloid Leukemia, Childhood Brain Stem Glioma, Childhood Cerebellar Astrocytoma, Childhood Cerebral Astrocytoma, Childhood Extracranial Germ Cell Tumors, Childhood Hodgkin's Disease, Childhood Hodgkin's Lymphoma, Childhood Hypothalamic and Visual Pathway Glioma, Childhood Lymphoblastic Leukemia, Childhood Medulloblastoma, Childhood Non-Hodgkin's Lymphoma, Childhood Pineal and Supratentorial Primitive Neuroectodermal Tumors, Childhood Primary Liver Cancer, Childhood Rhabdomyosarcoma, Childhood Soft Tissue Sarcoma, Childhood Visual Pathway and Hypothalamic Glioma, Chronic Lymphocytic Leukemia, Chronic Myelogenous Leukemia, Colon Cancer, Cutaneous T-Cell Lymphoma, Endocrine Pancreas Islet Cell Carcinoma, Endometrial Cancer, Ependymoma, Epithelial Cancer, Esophageal Cancer, Ewing's Sarcoma and Related Tumors, Exocrine Pancreatic Cancer, Extracranial Germ Cell Tumor, Extragonadal Germ Cell Tumor, Extrahepatic Bile Duct Cancer, Eye Cancer, Female Breast Cancer, Gaucher's Disease, Gallbladder Cancer, Gastric Cancer, Gastrointestinal Carcinoid Tumor, Gastrointestinal Tumors, Germ Cell Tumors, Gestational Trophoblastic Tumor, Hairy Cell Leukemia, Head and Neck Cancer, Hepatocellular Cancer, Hodgkin's Disease, Hodgkin's Lymphoma, Hypergammaglobulinemia, Hypopharyngeal Cancer, Intestinal Cancers, Intraocular Melanoma, Islet Cell Carcinoma, Islet Cell Pancreatic Cancer, Kaposi's Sarcoma, Kidney Cancer, Laryngeal Cancer, Lip and Oral Cavity Cancer, Liver Cancer, Lung Cancer, Lymphoproliferative Disorders, Macroglobulinemia, Male Breast Cancer, Malignant Mesothelioma, Malignant Thymoma, Medulloblastoma, Melanoma, Mesothelioma, Metastatic Occult Primary Squamous Neck Cancer, Metastatic Primary Squamous Neck Cancer, Metastatic Squamous Neck Cancer, Multiple Myeloma, Multiple Myeloma/Plasma Cell Neoplasm, Myelodysplastic Syndrome, Myelogenous Leukemia,

Myeloid Leukemia, Myeloproliferative Disorders, Nasal Cavity and Paranasal Sinus Cancer, Nasopharyngeal Cancer, Neuroblastoma, Non-Hodgkin's Lymphoma During Pregnancy, Nonmelanoma Skin Cancer, Non-Small Cell Lung Cancer, Occult Primary Metastatic Squamous Neck Cancer, Oropharyngeal Cancer, Osteo-/Malignant Fibrous Sarcoma, Osteosarcoma/Malignant Fibrous Histiocytoma, Osteosarcoma/Malignant Fibrous Histiocytoma of Bone, Ovarian Epithelial Cancer, Ovarian Germ Cell Tumor, Ovarian Low Malignant Potential Tumor, Pancreatic Cancer, Paraproteinemias, Purpura, Parathyroid Cancer, Penile Cancer, Pheochromocytoma, Pituitary Tumor, Plasma Cell Neoplasm/Multiple Myeloma, Primary Central Nervous System Lymphoma, Primary Liver Cancer, Prostate Cancer, Rectal Cancer, Renal Cell Cancer, Renal Pelvis and Ureter Cancer, Retinoblastoma, Rhabdomyosarcoma, Salivary Gland Cancer, Sarcoidosis Sarcomas, Sezary Syndrome, Skin Cancer, Small Cell Lung Cancer, Small Intestine Cancer, Soft Tissue Sarcoma, Squamous Neck Cancer, Stomach Cancer, Supratentorial Primitive Neuroectodermal and Pineal Tumors, T-Cell Lymphoma, Testicular Cancer, Thymoma, Thyroid Cancer, Transitional Cell Cancer of the Renal Pelvis and Ureter, Transitional Renal Pelvis and Ureter Cancer, Trophoblastic Tumors, Ureter and Renal Pelvis Cell Cancer, Urethral Cancer, Uterine Cancer, Uterine Sarcoma, Vaginal Cancer, Visual Pathway and Hypothalamic Glioma, Vulvar Cancer, Waldenstrom's Macroglobulinemia, Wilms' Tumor, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.

[686] In another preferred embodiment, polynucleotides or polypeptides, or agonists or antagonists of the present invention are used to diagnose, prognose, prevent, and/or treat premalignant conditions and to prevent progression to a neoplastic or malignant state, including but not limited to those disorders described above. Such uses are indicated in conditions known or suspected of preceding progression to neoplasia or cancer, in particular, where non-neoplastic cell growth consisting of hyperplasia, metaplasia, or most particularly, dysplasia has occurred (for review of such abnormal growth conditions, see Robbins and Angell, 1976, Basic Pathology, 2d Ed., W. B. Saunders Co., Philadelphia, pp. 68-79.)

[687] Hyperplasia is a form of controlled cell proliferation, involving an increase in cell number in a tissue or organ, without significant alteration in structure or function. Hyperplastic disorders which can be diagnosed, prognosed, prevented, and/or treated with compositions of the invention (including polynucleotides, polypeptides, agonists or

antagonists) include, but are not limited to, angiofollicular mediastinal lymph node hyperplasia, angiolymphoid hyperplasia with eosinophilia, atypical melanocytic hyperplasia, basal cell hyperplasia, benign giant lymph node hyperplasia, cementum hyperplasia, congenital adrenal hyperplasia, congenital sebaceous hyperplasia, cystic hyperplasia, cystic hyperplasia of the breast, denture hyperplasia, ductal hyperplasia, endometrial hyperplasia, fibromuscular hyperplasia, focal epithelial hyperplasia, gingival hyperplasia, inflammatory fibrous hyperplasia, inflammatory papillary hyperplasia, intravascular papillary endothelial hyperplasia, nodular hyperplasia of prostate, nodular regenerative hyperplasia, pseudoepitheliomatous hyperplasia, senile sebaceous hyperplasia, and verrucous hyperplasia.

[688] Metaplasia is a form of controlled cell growth in which one type of adult or fully differentiated cell substitutes for another type of adult cell. Metaplastic disorders which can be diagnosed, prognosed, prevented, and/or treated with compositions of the invention (including polynucleotides, polypeptides, agonists or antagonists) include, but are not limited to, agnogenic myeloid metaplasia, apocrine metaplasia, atypical metaplasia, autoparenchymatous metaplasia, connective tissue metaplasia, epithelial metaplasia, intestinal metaplasia, metaplastic anemia, metaplastic ossification, metaplastic polyps, myeloid metaplasia, primary myeloid metaplasia, secondary myeloid metaplasia, squamous metaplasia, squamous metaplasia of amnion, and symptomatic myeloid metaplasia.

[689] Dysplasia is frequently a forerunner of cancer, and is found mainly in the epithelia; it is the most disorderly form of non-neoplastic cell growth, involving a loss in individual cell uniformity and in the architectural orientation of cells. Dysplastic cells often have abnormally large, deeply stained nuclei, and exhibit pleomorphism. Dysplasia characteristically occurs where there exists chronic irritation or inflammation. Dysplastic disorders which can be diagnosed, prognosed, prevented, and/or treated with compositions of the invention (including polynucleotides, polypeptides, agonists or antagonists) include, but are not limited to, anhidrotic ectodermal dysplasia, anterofacial dysplasia, asphyxiating thoracic dysplasia, atriodigital dysplasia, bronchopulmonary dysplasia, cerebral dysplasia, cervical dysplasia, chondroectodermal dysplasia, cleidocranial dysplasia, congenital ectodermal dysplasia, craniodiaphysial dysplasia, craniocarpotarsal dysplasia, craniometaphysial dysplasia, dentin dysplasia, diaphysial dysplasia, ectodermal dysplasia, enamel dysplasia, encephalo-ophthalmic dysplasia, dysplasia epiphysialis hemimelia, dysplasia epiphysialis multiplex,

dysplasia epiphysialis punctata, epithelial dysplasia, faciodigitogenital dysplasia, familial fibrous dysplasia of jaws, familial white folded dysplasia, fibromuscular dysplasia, fibrous dysplasia of bone, florid osseous dysplasia, hereditary renal-retinal dysplasia, hidrotic ectodermal dysplasia, hypohidrotic ectodermal dysplasia, lymphopenic thymic dysplasia, mammary dysplasia, mandibulofacial dysplasia, metaphysial dysplasia, Mondini dysplasia, monostotic fibrous dysplasia, mucoepithelial dysplasia, multiple epiphysial dysplasia, oculoauriculovertebral dysplasia, oculodentodigital dysplasia, oculovertebral dysplasia, odontogenic dysplasia, ophthalmomandibulomelic dysplasia, periapical cemental dysplasia, polyostotic fibrous dysplasia, pseudoachondroplastic spondyloepiphysial dysplasia, retinal dysplasia, septo-optic dysplasia, spondyloepiphysial dysplasia, and ventriculoradial dysplasia.

[690] Additional pre-neoplastic disorders which can be diagnosed, prognosed, prevented, and/or treated with compositions of the invention (including polynucleotides, polypeptides, agonists or antagonists) include, but are not limited to, benign dysproliferative disorders (e.g., benign tumors, fibrocystic conditions, tissue hypertrophy, intestinal polyps, colon polyps, and esophageal dysplasia), leukoplakia, keratoses, Bowen's disease, Farmer's Skin, solar cheilitis, and solar keratosis.

[691] In another embodiment, a polypeptide of the invention, or polynucleotides, antibodies, agonists, or antagonists corresponding to that polypeptide, may be used to diagnose and/or prognose disorders associated with the tissue(s) in which the polypeptide of the invention is expressed, including one, two, three, four, five, or more tissues disclosed in Table 10, column 2 (Library Code).

[692] In another embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention conjugated to a toxin or a radioactive isotope, as described herein, may be used to treat cancers and neoplasms, including, but not limited to those described herein. In a further preferred embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention conjugated to a toxin or a radioactive isotope, as described herein, may be used to treat acute myelogenous leukemia.

[693] Additionally, polynucleotides, polypeptides, and/or agonists or antagonists of the invention may affect apoptosis, and therefore, would be useful in treating a number of diseases associated with increased cell survival or the inhibition of apoptosis. For example, diseases associated with increased cell survival or the inhibition of apoptosis that could be

diagnosed, prognosed, prevented, and/or treated by polynucleotides, polypeptides, and/or agonists or antagonists of the invention, include cancers (such as follicular lymphomas, carcinomas with p53 mutations, and hormone-dependent tumors, including, but not limited to colon cancer, cardiac tumors, pancreatic cancer, melanoma, retinoblastoma, glioblastoma, lung cancer, intestinal cancer, testicular cancer, stomach cancer, neuroblastoma, myxoma, myoma, lymphoma, endothelioma, osteoblastoma, osteoclastoma, osteosarcoma, chondrosarcoma, adenoma, breast cancer, prostate cancer, Kaposi's sarcoma and ovarian cancer); autoimmune disorders such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) and viral infections (such as herpes viruses, pox viruses and adenoviruses), inflammation, graft v. host disease, acute graft rejection, and chronic graft rejection.

[694] In preferred embodiments, polynucleotides, polypeptides, and/or agonists or antagonists of the invention are used to inhibit growth, progression, and/or metastasis of cancers, in particular those listed above.

[695] Additional diseases or conditions associated with increased cell survival that could be diagnosed, prognosed, prevented, and/or treated by polynucleotides, polypeptides, and/or agonists or antagonists of the invention, include, but are not limited to, progression, and/or metastases of malignancies and related disorders such as leukemia (including acute leukemias (e.g., acute lymphocytic leukemia, acute myelocytic leukemia (including myeloblastic, promyelocytic, myelomonocytic, monocytic, and erythroleukemia)) and chronic leukemias (e.g., chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia)), polycythemia vera, lymphomas (e.g., Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, and solid tumors including, but not limited to, sarcomas and carcinomas such as fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma,

choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, emangioblastoma, acoustic neuroma, oligodendroglioma, menangioma, melanoma, neuroblastoma, and retinoblastoma.

[696] Diseases associated with increased apoptosis that could be diagnosed, prognosed, prevented, and/or treated by polynucleotides, polypeptides, and/or agonists or antagonists of the invention, include AIDS; neurodegenerative disorders (such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, retinitis pigmentosa, cerebellar degeneration and brain tumor or prior associated disease); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) myelodysplastic syndromes (such as aplastic anemia), graft v. host disease, ischemic injury (such as that caused by myocardial infarction, stroke and reperfusion injury), liver injury (e.g., hepatitis related liver injury, ischemia/reperfusion injury, cholestosis (bile duct injury) and liver cancer); toxin-induced liver disease (such as that caused by alcohol), septic shock, cachexia and anorexia.

[697] Hyperproliferative diseases and/or disorders that could be diagnosed, prognosed, prevented, and/or treated by polynucleotides, polypeptides, and/or agonists or antagonists of the invention, include, but are not limited to, neoplasms located in the liver, abdomen, bone, breast, digestive system, pancreas, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous system (central and peripheral), lymphatic system, pelvis, skin, soft tissue, spleen, thorax, and urogenital tract.

[698] Similarly, other hyperproliferative disorders can also be diagnosed, prognosed, prevented, and/or treated by polynucleotides, polypeptides, and/or agonists or antagonists of the invention. Examples of such hyperproliferative disorders include, but are not limited to: hypergammaglobulinemia, lymphoproliferative disorders, paraproteinemias, purpura, sarcoidosis, Sezary Syndrome, Waldenstron's macroglobulinemia, Gaucher's Disease, histiocytosis, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.

[699] Another preferred embodiment utilizes polynucleotides of the present invention to inhibit aberrant cellular division, by gene therapy using the present invention, and/or protein fusions or fragments thereof.

[700] Thus, the present invention provides a method for treating cell proliferative disorders by inserting into an abnormally proliferating cell a polynucleotide of the present invention, wherein said polynucleotide represses said expression.

[701] Another embodiment of the present invention provides a method of treating cell-proliferative disorders in individuals comprising administration of one or more active gene copies of the present invention to an abnormally proliferating cell or cells. In a preferred embodiment, polynucleotides of the present invention is a DNA construct comprising a recombinant expression vector effective in expressing a DNA sequence encoding said polynucleotides. In another preferred embodiment of the present invention, the DNA construct encoding the poynucleotides of the present invention is inserted into cells to be treated utilizing a retrovirus, or more preferably an adenoviral vector (See G J. Nabel, et. al., PNAS 1999 96: 324-326, which is hereby incorporated by reference). In a most preferred embodiment, the viral vector is defective and will not transform non-proliferating cells, only proliferating cells. Moreover, in a preferred embodiment, the polynucleotides of the present invention inserted into proliferating cells either alone, or in combination with or fused to other polynucleotides, can then be modulated via an external stimulus (i.e. magnetic, specific small molecule, chemical, or drug administration, etc.), which acts upon the promoter upstream of said polynucleotides to induce expression of the encoded protein product. As such the beneficial therapeutic affect of the present invention may be expressly modulated (i.e. to increase, decrease, or inhibit expression of the present invention) based upon said external stimulus.

[702] Polynucleotides of the present invention may be useful in repressing expression of oncogenic genes or antigens. By "repressing expression of the oncogenic genes " is intended the suppression of the transcription of the gene, the degradation of the gene transcript (pre-message RNA), the inhibition of splicing, the destruction of the messenger RNA, the prevention of the post-translational modifications of the protein, the destruction of the protein, or the inhibition of the normal function of the protein.

[703] For local administration to abnormally proliferating cells, polynucleotides of the present invention may be administered by any method known to those of skill in the art

including, but not limited to transfection, electroporation, microinjection of cells, or in vehicles such as liposomes, lipofectin, or as naked polynucleotides, or any other method described throughout the specification. The polynucleotide of the present invention may be delivered by known gene delivery systems such as, but not limited to, retroviral vectors (Gilboa, J. Virology 44:845 (1982); Hocke, Nature 320:275 (1986); Wilson, et al., Proc. Natl. Acad. Sci. U.S.A. 85:3014), vaccinia virus system (Chakrabarty et al., Mol. Cell Biol. 5:3403 (1985) or other efficient DNA delivery systems (Yates et al., Nature 313:812 (1985)) known to those skilled in the art. These references are exemplary only and are hereby incorporated by reference. In order to specifically deliver or transfect cells which are abnormally proliferating and spare non-dividing cells, it is preferable to utilize a retrovirus, or adenoviral (as described in the art and elsewhere herein) delivery system known to those of skill in the art. Since host DNA replication is required for retroviral DNA to integrate and the retrovirus will be unable to self replicate due to the lack of the retrovirus genes needed for its life cycle. Utilizing such a retroviral delivery system for polynucleotides of the present invention will target said gene and constructs to abnormally proliferating cells and will spare the non-dividing normal cells.

[704] The polynucleotides of the present invention may be delivered directly to cell proliferative disorder/disease sites in internal organs, body cavities and the like by use of imaging devices used to guide an injecting needle directly to the disease site. The polynucleotides of the present invention may also be administered to disease sites at the time of surgical intervention.

[705] By "cell proliferative disease" is meant any human or animal disease or disorder, affecting any one or any combination of organs, cavities, or body parts, which is characterized by single or multiple local abnormal proliferations of cells, groups of cells, or tissues, whether benign or malignant.

[706] Any amount of the polynucleotides of the present invention may be administered as long as it has a biologically inhibiting effect on the proliferation of the treated cells. Moreover, it is possible to administer more than one of the polynucleotide of the present invention simultaneously to the same site. By "biologically inhibiting" is meant partial or total growth inhibition as well as decreases in the rate of proliferation or growth of the cells. The biologically inhibitory dose may be determined by assessing the effects of the polynucleotides of the present invention on target malignant or abnormally proliferating cell

growth in tissue culture, tumor growth in animals and cell cultures, or any other method known to one of ordinary skill in the art.

[707] The present invention is further directed to antibody-based therapies which involve administering of anti-polypeptides and anti-polynucleotide antibodies to a mammalian, preferably human, patient for treating one or more of the described disorders. Methods for producing anti-polypeptides and anti-polynucleotide antibodies polyclonal and monoclonal antibodies are described in detail elsewhere herein. Such antibodies may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

[708] A summary of the ways in which the antibodies of the present invention may be used therapeutically includes binding polynucleotides or polypeptides of the present invention locally or systemically in the body or by direct cytotoxicity of the antibody, e.g. as mediated by complement (CDC) or by effector cells (ADCC). Some of these approaches are described in more detail below. Armed with the teachings provided herein, one of ordinary skill in the art will know how to use the antibodies of the present invention for diagnostic, monitoring or therapeutic purposes without undue experimentation.

[709] In particular, the antibodies, fragments and derivatives of the present invention are useful for treating a subject having or developing cell proliferative and/or differentiation disorders as described herein. Such treatment comprises administering a single or multiple doses of the antibody, or a fragment, derivative, or a conjugate thereof.

[710] The antibodies of this invention may be advantageously utilized in combination with other monoclonal or chimeric antibodies, or with lymphokines or hematopoietic growth factors, for example., which serve to increase the number or activity of effector cells which interact with the antibodies.

[711] It is preferred to use high affinity and/or potent *in vivo* inhibiting and/or neutralizing antibodies against polypeptides or polynucleotides of the present invention, fragments or regions thereof, for both immunoassays directed to and therapy of disorders related to polynucleotides or polypeptides, including fragements thereof, of the present invention. Such antibodies, fragments, or regions, will preferably have an affinity for polynucleotides or polypeptides, including fragements thereof. Preferred binding affinities include those with a dissociation constant or Kd less than $5X10^{-6}M$, $10^{-6}M$, $5X10^{-7}M$, $10^{-7}M$, $5X10^{-8}M$, $10^{-8}M$, $5X10^{-9}M$, $10^{-9}M$, $5X10^{-10}M$, $10^{-10}M$, $5X10^{-11}M$, $10^{-11}M$, $5X10^{-12}M$, $10^{-12}M$, $5X10^{-13}M$, $10^{-13}M$, $5X10^{-14}M$, $10^{-14}M$, $5X10^{-15}M$, and $10^{-15}M$.

[712] Moreover, polypeptides of the present invention are useful in inhibiting the angiogenesis of proliferative cells or tissues, either alone, as a protein fusion, or in combination with other polypeptides directly or indirectly, as described elsewhere herein. In a most preferred embodiment, said anti-angiogenesis effect may be achieved indirectly, for example, through the inhibition of hematopoietic, tumor-specific cells, such as tumor-associated macrophages (See Joseph IB, et al. J Natl Cancer Inst, 90(21):1648-53 (1998), which is hereby incorporated by reference). Antibodies directed to polypeptides or polynucleotides of the present invention may also result in inhibition of angiogenesis directly, or indirectly (See Witte L, et al., Cancer Metastasis Rev. 17(2):155-61 (1998), which is hereby incorporated by reference)).

[713] Polypeptides, including protein fusions, of the present invention, or fragments thereof may be useful in inhibiting proliferative cells or tissues through the induction of apoptosis. Said polypeptides may act either directly, or indirectly to induce apoptosis of proliferative cells and tissues, for example in the activation of a death-domain receptor, such as tumor necrosis factor (TNF) receptor-1, CD95 (Fas/APO-1), TNF-receptor-related apoptosis-mediated protein (TRAMP) and TNF-related apoptosis-inducing ligand (TRAIL) receptor-1 and -2 (See Schulze-Osthoff K, et.al., Eur J Biochem 254(3):439-59 (1998), which is hereby incorporated by reference). Moreover, in another preferred embodiment of the present invention, said polypeptides may induce apoptosis through other mechanisms, such as in the activation of other proteins which will activate apoptosis, or through stimulating the expression of said proteins, either alone or in combination with small molecule drugs or adjuviants, such as apoptonin, galectins, thioredoxins, anti-inflammatory proteins (See for example, Mutat Res 400(1-2):447-55 (1998), Med Hypotheses.50(5):423-33 (1998), Chem Biol Interact. Apr 24;111-112:23-34 (1998), J Mol Med.76(6):402-12 (1998), Int J Tissue React;20(1):3-15 (1998), which are all hereby incorporated by reference).

[714] Polypeptides, including protein fusions to, or fragments thereof, of the present invention are useful in inhibiting the metastasis of proliferative cells or tissues. Inhibition may occur as a direct result of administering polypeptides, or antibodies directed to said polypeptides as described elsewere herein, or indirectly, such as activating the expression of proteins known to inhibit metastasis, for example alpha 4 integrins, (See, e.g., Curr Top Microbiol Immunol 1998;231:125-41, which is hereby incorporated by reference). Such

thereapeutic affects of the present invention may be achieved either alone, or in combination with small molecule drugs or adjuvants.

[715] In another embodiment, the invention provides a method of delivering compositions containing the polypeptides of the invention (e.g., compositions containing polypeptides or polypeptide antibodes associated with heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs) to targeted cells expressing the polypeptide of the present invention. Polypeptides or polypeptide antibodes of the invention may be associated with with heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs via hydrophobic, hydrophilic, ionic and/or covalent interactions.

[716] Polypeptides, protein fusions to, or fragments thereof, of the present invention are useful in enhancing the immunogenicity and/or antigenicity of proliferating cells or tissues, either directly, such as would occur if the polypeptides of the present invention 'vaccinated' the immune response to respond to proliferative antigens and immunogens, or indirectly, such as in activating the expression of proteins known to enhance the immune response (e.g. chemokines), to said antigens and immunogens.

Renal Disorders

[717] Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention, may be used to treat, prevent, diagnose, and/or prognose disorders of the renal system. Renal disorders which can be diagnosed, prognosed, prevented, and/or treated with compositions of the invention include, but are not limited to, kidney failure, nephritis, blood vessel disorders of kidney, metabolic and congenital kidney disorders, urinary disorders of the kidney, autoimmune disorders, sclerosis and necrosis, electrolyte imbalance, and kidney cancers.

[718] Kidney diseases which can be diagnosed, prognosed, prevented, and/or treated with compositions of the invention include, but are not limited to, acute kidney failure, chronic kidney failure, atheroembolic renal failure, end-stage renal disease, inflammatory diseases of the kidney (e.g., acute glomerulonephritis, postinfectious glomerulonephritis, rapidly progressive glomerulonephritis, nephrotic syndrome, membranous glomerulonephritis, familial nephrotic syndrome, membranoproliferative glomerulonephritis I and II, mesangial proliferative glomerulonephritis, chronic glomerulonephritis, acute

tubulointerstitial nephritis, chronic tubulointerstitial nephritis, acute post-streptococcal glomerulonephritis (PSGN), pyelonephritis, lupus nephritis, chronic nephritis, interstitial nephritis, and post-streptococcal glomerulonephritis), blood vessel disorders of the kidneys (e.g., kidney infarction, atheroembolic kidney disease, cortical necrosis, malignant nephrosclerosis, renal vein thrombosis, renal underperfusion, renal retinopathy, renal ischemia-reperfusion, renal artery embolism, and renal artery stenosis), and kidney disorders resulting form urinary tract disease (e.g., pyelonephritis, hydronephrosis, urolithiasis (renal lithiasis, nephrolithiasis), reflux nephropathy, urinary tract infections, urinary retention, and acute or chronic unilateral obstructive uropathy.)

[719] In addition, compositions of the invention can be used to diagnose, prognose, prevent, and/or treat metabolic and congenital disorders of the kidney (e.g., uremia, renal amyloidosis, renal osteodystrophy, renal tubular acidosis, renal glycosuria, nephrogenic diabetes insipidus, cystinuria, Fanconi's syndrome, renal fibrocystic osteosis (renal rickets), Hartnup disease, Bartter's syndrome, Liddle's syndrome, polycystic kidney disease, medullary cystic disease, medullary sponge kidney, Alport's syndrome, nail-patella syndrome, congenital nephrotic syndrome, CRUSH syndrome, horseshoe kidney, diabetic nephropathy, nephrogenic diabetes insipidus, analgesic nephropathy, kidney stones, and membranous nephropathy), and autoimmune disorders of the kidney (e.g., systemic lupus erythematosus (SLE), Goodpasture syndrome, IgA nephropathy, and IgM mesangial proliferative glomerulonephritis).

[720] Compositions of the invention can also be used to diagnose, prognose, prevent, and/or treat sclerotic or necrotic disorders of the kidney (e.g., glomerulosclerosis, diabetic nephropathy, focal segmental glomerulosclerosis (FSGS), necrotizing glomerulonephritis, and renal papillary necrosis), cancers of the kidney (e.g., nephroma, hypernephroma, nephroblastoma, renal cell cancer, transitional cell cancer, renal adenocarcinoma, squamous cell cancer, and Wilm's tumor), and electrolyte imbalances (e.g., nephrocalcinosis, pyuria, edema, hydronephritis, proteinuria, hyponatremia, hypernatremia, hypokalemia, hyperkalemia, hypocalcemia, hypercalcemia, hypophosphatemia, and hyperphosphatemia).

[721] Polypeptides may be administered using any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, biolistic injectors, particle accelerators, gelfoam sponge depots, other commercially available depot materials, osmotic pumps, oral or suppositorial

solid pharmaceutical formulations, decanting or topical applications during surgery, aerosol delivery. Such methods are known in the art. Polypeptides may be administered as part of a Therapeutic, described in more detail below. Methods of delivering polynucleotides are described in more detail herein.

Cardiovascular Disorders

[722] Polynucleotides or polypeptides, or agonists or antagonists of the present invention, may be used to treat, prevent, diagnose, and/or prognose cardiovascular disorders, including, but not limited to, peripheral artery disease, such as limb ischemia.

[723] Cardiovascular disorders include, but are not limited to, cardiovascular abnormalities, such as arterio-arterial fistula, arteriovenous fistula, cerebral arteriovenous malformations, congenital heart defects, pulmonary atresia, and Scimitar Syndrome. Congenital heart defects include, but are not limited to, aortic coarctation, cor triatriatum, coronary vessel anomalies, crisscross heart, dextrocardia, patent ductus arteriosus, Ebstein's anomaly, Eisenmenger complex, hypoplastic left heart syndrome, levocardia, tetralogy of fallot, transposition of great vessels, double outlet right ventricle, tricuspid atresia, persistent truncus arteriosus, and heart septal defects, such as aortopulmonary septal defect, endocardial cushion defects, Lutembacher's Syndrome, trilogy of Fallot, ventricular heart septal defects.

[724] Cardiovascular disorders also include, but are not limited to, heart disease, such as arrhythmias, carcinoid heart disease, high cardiac output, low cardiac output, cardiac tamponade, endocarditis (including bacterial), heart aneurysm, cardiac arrest, congestive heart failure, congestive cardiomyopathy, paroxysmal dyspnea, cardiac edema, heart hypertrophy, congestive cardiomyopathy, left ventricular hypertrophy, right ventricular hypertrophy, post-infarction heart rupture, ventricular septal rupture, heart valve diseases, myocardial diseases, myocardial ischemia, pericardial effusion, pericarditis (including constrictive and tuberculous), pneumopericardium, postpericardiotomy syndrome, pulmonary heart disease, rheumatic heart disease, ventricular dysfunction, hyperemia, cardiovascular pregnancy complications, Scimitar Syndrome, cardiovascular syphilis, and cardiovascular tuberculosis.

[725] Arrhythmias include, but are not limited to, sinus arrhythmia, atrial fibrillation, atrial flutter, bradycardia, extrasystole, Adams-Stokes Syndrome, bundle-branch block,

sinoatrial block, long QT syndrome, parasystole, Lown-Ganong-Levine Syndrome, Mahaim-type pre-excitation syndrome, Wolff-Parkinson-White syndrome, sick sinus syndrome, tachycardias, and ventricular fibrillation. Tachycardias include paroxysmal tachycardia, supraventricular tachycardia, accelerated idioventricular rhythm, atrioventricular nodal reentry tachycardia, ectopic atrial tachycardia, ectopic junctional tachycardia, sinoatrial nodal reentry tachycardia, sinus tachycardia, Torsades de Pointes, and ventricular tachycardia.

[726] Heart valve diseases include, but are not limited to, aortic valve insufficiency, aortic valve stenosis, hear murmurs, aortic valve prolapse, mitral valve prolapse, tricuspid valve prolapse, mitral valve insufficiency, mitral valve stenosis, pulmonary atresia, pulmonary valve insufficiency, pulmonary valve stenosis, tricuspid atresia, tricuspid valve insufficiency, and tricuspid valve stenosis.

[727] Myocardial diseases include, but are not limited to, alcoholic cardiomyopathy, congestive cardiomyopathy, hypertrophic cardiomyopathy, aortic subvalvular stenosis, pulmonary subvalvular stenosis, restrictive cardiomyopathy, Chagas cardiomyopathy, endocardial fibroelastosis, endomyocardial fibrosis, Kearns Syndrome, myocardial reperfusion injury, and myocarditis.

[728] Myocardial ischemias include, but are not limited to, coronary disease, such as angina pectoris, coronary aneurysm, coronary arteriosclerosis, coronary thrombosis, coronary vasospasm, myocardial infarction and myocardial stunning.

[729] Cardiovascular diseases also include vascular diseases such as aneurysms, angiodysplasia, angiomatosis, bacillary angiomatosis, Hippel-Lindau Disease, Klippel-Trenaunay-Weber Syndrome, Sturge-Weber Syndrome, angioneurotic edema, aortic diseases, Takayasu's Arteritis, aortitis, Leriche's Syndrome, arterial occlusive diseases, arteritis, enarteritis, polyarteritis nodosa, cerebrovascular disorders, diabetic angiopathies, diabetic retinopathy, embolisms, thrombosis, erythromelalgia, hemorrhoids, hepatic veno-occlusive disease, hypertension, hypotension, ischemia, peripheral vascular diseases, phlebitis, pulmonary veno-occlusive disease, Raynaud's disease, CREST syndrome, retinal vein occlusion, Scimitar syndrome, superior vena cava syndrome, telangiectasia, atacia telangiectasia, hereditary hemorrhagic telangiectasia, varicocele, varicose veins, varicose ulcer, vasculitis, and venous insufficiency.

[730] Aneurysms include, but are not limited to, dissecting aneurysms, false aneurysms, infected aneurysms, ruptured aneurysms, aortic aneurysms, cerebral aneurysms, coronary aneurysms, heart aneurysms, and iliac aneurysms.

[731] Arterial occlusive diseases include, but are not limited to, arteriosclerosis, intermittent claudication, carotid stenosis, fibromuscular dysplasias, mesenteric vascular occlusion, Moyamoya disease, renal artery obstruction, retinal artery occlusion, and thromboangiitis obliterans.

[732] Cerebrovascular disorders include, but are not limited to, carotid artery diseases, cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformation, cerebral artery diseases, cerebral embolism and thrombosis, carotid artery thrombosis, sinus thrombosis, Wallenberg's syndrome, cerebral hemorrhage, epidural hematoma, subdural hematoma, subaraxhnoid hemorrhage, cerebral infarction, cerebral ischemia (including transient), subclavian steal syndrome, periventricular leukomalacia, vascular headache, cluster headache, migraine, and vertebrobasilar insufficiency.

[733] Embolisms include, but are not limited to, air embolisms, amniotic fluid embolisms, cholesterol embolisms, blue toe syndrome, fat embolisms, pulmonary embolisms, and thromoboembolisms. Thrombosis include, but are not limited to, coronary thrombosis, hepatic vein thrombosis, retinal vein occlusion, carotid artery thrombosis, sinus thrombosis, Wallenberg's syndrome, and thrombophlebitis.

[734] Ischemic disorders include, but are not limited to, cerebral ischemia, ischemic colitis, compartment syndromes, anterior compartment syndrome, myocardial ischemia, reperfusion injuries, and peripheral limb ischemia. Vasculitis includes, but is not limited to, aortitis, arteritis, Behcet's Syndrome, Churg-Strauss Syndrome, mucocutaneous lymph node syndrome, thromboangiitis obliterans, hypersensitivity vasculitis, Schoenlein-Henoch purpura, allergic cutaneous vasculitis, and Wegener's granulomatosis.

[735] Polypeptides may be administered using any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, biolistic injectors, particle accelerators, gelfoam sponge depots, other commercially available depot materials, osmotic pumps, oral or suppositorial solid pharmaceutical formulations, decanting or topical applications during surgery, aerosol delivery. Such methods are known in the art. Polypeptides may be administered as part of a

Therapeutic, described in more detail below. Methods of delivering polynucleotides are described in more detail herein.

Respiratory Disorders

[736] Polynucleotides or polypeptides, or agonists or antagonists of the present invention may be used to treat, prevent, diagnose, and/or prognose diseases and/or disorders of the respiratory system.

[737] Diseases and disorders of the respiratory system include, but are not limited to, nasal vestibulitis, nonallergic rhinitis (e.g., acute rhinitis, chronic rhinitis, atrophic rhinitis, vasomotor rhinitis), nasal polyps, and sinusitis, juvenile angiofibromas, cancer of the nose and juvenile papillomas, vocal cord polyps, nodules (singer's nodules), contact ulcers, vocal cord paralysis, laryngoceles, pharyngitis (e.g., viral and bacterial), tonsillitis, tonsillar cellulitis, parapharyngeal abscess, laryngitis, laryngoceles, and throat cancers (e.g., cancer of the nasopharynx, tonsil cancer, larynx cancer), lung cancer (e.g., squamous cell carcinoma, small cell (oat cell) carcinoma, large cell carcinoma, and adenocarcinoma), allergic disorders (eosinophilic pneumonia, hypersensitivity pneumonitis (e.g., extrinsic allergic alveolitis, allergic interstitial pneumonitis, organic dust pneumoconiosis, allergic bronchopulmonary aspergillosis, asthma, Wegener's granulomatosis (granulomatous vasculitis), Goodpasture's syndrome)), pneumonia (e.g., bacterial pneumonia (e.g., *Streptococcus pneumoniae* (pneumoncoccal pneumonia), *Staphylococcus aureus* (staphylococcal pneumonia), Gram-negative bacterial pneumonia (caused by, e.g., *Klebsiella* and *Pseudomas spp.*), *Mycoplasma pneumoniae* pneumonia, *Hemophilus influenzae* pneumonia, *Legionella pneumophila* (Legionnaires' disease), and *Chlamydia psittaci* (Psittacosis)), and viral pneumonia (e.g., influenza, chickenpox (varicella).

[738] Additional diseases and disorders of the respiratory system include, but are not limited to bronchiolitis, polio (poliomyelitis), croup, respiratory syncytial viral infection, mumps, erythema infectiosum (fifth disease), roseola infantum, progressive rubella panencephalitis, german measles, and subacute sclerosing panencephalitis), fungal pneumonia (e.g., Histoplasmosis, Coccidioidomycosis, Blastomycosis, fungal infections in people with severely suppressed immune systems (e.g., cryptococcosis, caused by *Cryptococcus neoformans*; aspergillosis, caused by *Aspergillus spp.*; candidiasis, caused by

Candida; and mucormycosis)), *Pneumocystis carinii* (pneumocystis pneumonia), atypical pneumonias (e.g., *Mycoplasma* and *Chlamydia* spp.), opportunistic infection pneumonia, nosocomial pneumonia, chemical pneumonitis, and aspiration pneumonia, pleural disorders (e.g., pleurisy, pleural effusion, and pneumothorax (e.g., simple spontaneous pneumothorax, complicated spontaneous pneumothorax, tension pneumothorax)), obstructive airway diseases (e.g., asthma, chronic obstructive pulmonary disease (COPD), emphysema, chronic or acute bronchitis), occupational lung diseases (e.g., silicosis, black lung (coal workers' pneumoconiosis), asbestosis, berylliosis, occupational asthsma, byssinosis, and benign pneumoconioses), Infiltrative Lung Disease (e.g., pulmonary fibrosis (e.g., fibrosing alveolitis, usual interstitial pneumonia), idiopathic pulmonary fibrosis, desquamative interstitial pneumonia, lymphoid interstitial pneumonia, histiocytosis X (e.g., Letterer-Siwe disease, Hand-Schüller-Christian disease, eosinophilic granuloma), idiopathic pulmonary hemosiderosis, sarcoidosis and pulmonary alveolar proteinosis), Acute respiratory distress syndrome (also called, e.g., adult respiratory distress syndrome), edema, pulmonary embolism, bronchitis (e.g., viral, bacterial), bronchiectasis, atelectasis, lung abscess (caused by, e.g., *Staphylococcus aureus* or *Legionella pneumophila*), and cystic fibrosis.

Anti-Angiogenesis Activity

[739] The naturally occurring balance between endogenous stimulators and inhibitors of angiogenesis is one in which inhibitory influences predominate. Rastinejad *et al., Cell* *56*:345-355 (1989). In those rare instances in which neovascularization occurs under normal physiological conditions, such as wound healing, organ regeneration, embryonic development, and female reproductive processes, angiogenesis is stringently regulated and spatially and temporally delimited. Under conditions of pathological angiogenesis such as that characterizing solid tumor growth, these regulatory controls fail. Unregulated angiogenesis becomes pathologic and sustains progression of many neoplastic and non-neoplastic diseases. A number of serious diseases are dominated by abnormal neovascularization including solid tumor growth and metastases, arthritis, some types of eye disorders, and psoriasis. See, e.g., reviews by Moses *et al., Biotech.* *9*:630-634 (1991); Folkman *et al., N. Engl. J. Med., 333*:1757-1763 (1995); Auerbach *et al., J. Microvasc. Res.* *29*:401-411 (1985); Folkman, Advances in Cancer Research, eds. Klein and Weinhouse,

Academic Press, New York, pp. 175-203 (1985); Patz, *Am. J. Opthalmol. 94*:715-743 (1982); and Folkman *et al.,* Science *221*:719-725 (1983). In a number of pathological conditions, the process of angiogenesis contributes to the disease state. For example, significant data have accumulated which suggest that the growth of solid tumors is dependent on angiogenesis. Folkman and Klagsbrun, *Science 235*:442-447 (1987).

[740] The present invention provides for treatment of diseases or disorders associated with neovascularization by administration of the polynucleotides and/or polypeptides of the invention, as well as agonists or antagonists of the present invention. Malignant and metastatic conditions which can be treated with the polynucleotides and polypeptides, or agonists or antagonists of the invention include, but are not limited to, malignancies, solid tumors, and cancers described herein and otherwise known in the art (for a review of such disorders, see Fishman *et al.,* Medicine, 2d Ed., J. B. Lippincott Co., Philadelphia (1985)).Thus, the present invention provides a method of treating an angiogenesis-related disease and/or disorder, comprising administering to an individual in need thereof a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist of the invention. For example, polynucleotides, polypeptides, antagonists and/or agonists may be utilized in a variety of additional methods in order to therapeutically treat a cancer or tumor. Cancers which may be treated with polynucleotides, polypeptides, antagonists and/or agonists include, but are not limited to solid tumors, including prostate, lung, breast, ovarian, stomach, pancreas, larynx, esophagus, testes, liver, parotid, biliary tract, colon, rectum, cervix, uterus, endometrium, kidney, bladder, thyroid cancer; primary tumors and metastases; melanomas; glioblastoma; Kaposi's sarcoma; leiomyosarcoma; non- small cell lung cancer; colorectal cancer; advanced malignancies; and blood born tumors such as leukemias. For example, polynucleotides, polypeptides, antagonists and/or agonists may be delivered topically, in order to treat cancers such as skin cancer, head and neck tumors, breast tumors, and Kaposi's sarcoma.

[741] Within yet other aspects, polynucleotides, polypeptides, antagonists and/or agonists may be utilized to treat superficial forms of bladder cancer by, for example, intravesical administration. Polynucleotides, polypeptides, antagonists and/or agonists may be delivered directly into the tumor, or near the tumor site, via injection or a catheter. Of course, as the artisan of ordinary skill will appreciate, the appropriate mode of administration will vary according to the cancer to be treated. Other modes of delivery are discussed herein.

[742] Polynucleotides, polypeptides, antagonists and/or agonists may be useful in treating other disorders, besides cancers, which involve angiogenesis. These disorders include, but are not limited to: benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas; artheroscleric plaques; ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, uvietis and Pterygia (abnormal blood vessel growth) of the eye; rheumatoid arthritis; psoriasis; delayed wound healing; endometriosis; vasculogenesis; granulations; hypertrophic scars (keloids); nonunion fractures; scleroderma; trachoma; vascular adhesions; myocardial angiogenesis; coronary collaterals; cerebral collaterals; arteriovenous malformations; ischemic limb angiogenesis; Osler-Webber Syndrome; plaque neovascularization; telangiectasia; hemophiliac joints; angiofibroma; fibromuscular dysplasia; wound granulation; Crohn's disease; and atherosclerosis.

[743] For example, within one aspect of the present invention methods are provided for treating hypertrophic scars and keloids, comprising the step of administering a polynucleotide, polypeptide, antagonist and/or agonist of the invention to a hypertrophic scar or keloid.

[744] Within one embodiment of the present invention polynucleotides, polypeptides, antagonists and/or agonists of the invention are directly injected into a hypertrophic scar or keloid, in order to prevent the progression of these lesions. This therapy is of particular value in the prophylactic treatment of conditions which are known to result in the development of hypertrophic scars and keloids (e.g., burns), and is preferably initiated after the proliferative phase has had time to progress (approximately 14 days after the initial injury), but before hypertrophic scar or keloid development. As noted above, the present invention also provides methods for treating neovascular diseases of the eye, including for example, corneal neovascularization, neovascular glaucoma, proliferative diabetic retinopathy, retrolental fibroplasia and macular degeneration.

[745] Moreover, Ocular disorders associated with neovascularization which can be treated with the polynucleotides and polypeptides of the present invention (including agonists and/or antagonists) include, but are not limited to: neovascular glaucoma, diabetic retinopathy, retinoblastoma, retrolental fibroplasia, uveitis, retinopathy of prematurity macular degeneration, corneal graft neovascularization, as well as other eye inflammatory

diseases, ocular tumors and diseases associated with choroidal or iris neovascularization. See, e.g., reviews by Waltman *et al., Am. J. Ophthal. 85*:704-710 (1978) and Gartner *et al., Surv. Ophthal. 22*:291-312 (1978).

[746] Thus, within one aspect of the present invention methods are provided for treating neovascular diseases of the eye such as corneal neovascularization (including corneal graft neovascularization), comprising the step of administering to a patient a therapeutically effective amount of a compound (as described above) to the cornea, such that the formation of blood vessels is inhibited. Briefly, the cornea is a tissue which normally lacks blood vessels. In certain pathological conditions however, capillaries may extend into the cornea from the pericorneal vascular plexus of the limbus. When the cornea becomes vascularized, it also becomes clouded, resulting in a decline in the patient's visual acuity. Visual loss may become complete if the cornea completely opacitates. A wide variety of disorders can result in corneal neovascularization, including for example, corneal infections (e.g., trachoma, herpes simplex keratitis, leishmaniasis and onchocerciasis), immunological processes (e.g., graft rejection and Stevens-Johnson's syndrome), alkali burns, trauma, inflammation (of any cause), toxic and nutritional deficiency states, and as a complication of wearing contact lenses.

[747] Within particularly preferred embodiments of the invention, may be prepared for topical administration in saline (combined with any of the preservatives and antimicrobial agents commonly used in ocular preparations), and administered in eyedrop form. The solution or suspension may be prepared in its pure form and administered several times daily. Alternatively, anti-angiogenic compositions, prepared as described above, may also be administered directly to the cornea. Within preferred embodiments, the anti-angiogenic composition is prepared with a muco-adhesive polymer which binds to cornea. Within further embodiments, the anti-angiogenic factors or anti-angiogenic compositions may be utilized as an adjunct to conventional steroid therapy. Topical therapy may also be useful prophylactically in corneal lesions which are known to have a high probability of inducing an angiogenic response (such as chemical burns). In these instances the treatment, likely in combination with steroids, may be instituted immediately to help prevent subsequent complications.

[748] Within other embodiments, the compounds described above may be injected directly into the corneal stroma by an ophthalmologist under microscopic guidance. The

preferred site of injection may vary with the morphology of the individual lesion, but the goal of the administration would be to place the composition at the advancing front of the vasculature (i.e., interspersed between the blood vessels and the normal cornea). In most cases this would involve perilimbic corneal injection to "protect" the cornea from the advancing blood vessels. This method may also be utilized shortly after a corneal insult in order to prophylactically prevent corneal neovascularization. In this situation the material could be injected in the perilimbic cornea interspersed between the corneal lesion and its undesired potential limbic blood supply. Such methods may also be utilized in a similar fashion to prevent capillary invasion of transplanted corneas. In a sustained-release form injections might only be required 2-3 times per year. A steroid could also be added to the injection solution to reduce inflammation resulting from the injection itself.

[749] Within another aspect of the present invention, methods are provided for treating neovascular glaucoma, comprising the step of administering to a patient a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist to the eye, such that the formation of blood vessels is inhibited. In one embodiment, the compound may be administered topically to the eye in order to treat early forms of neovascular glaucoma. Within other embodiments, the compound may be implanted by injection into the region of the anterior chamber angle. Within other embodiments, the compound may also be placed in any location such that the compound is continuously released into the aqueous humor. Within another aspect of the present invention, methods are provided for treating proliferative diabetic retinopathy, comprising the step of administering to a patient a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist to the eyes, such that the formation of blood vessels is inhibited.

[750] Within particularly preferred embodiments of the invention, proliferative diabetic retinopathy may be treated by injection into the aqueous humor or the vitreous, in order to increase the local concentration of the polynucleotide, polypeptide, antagonist and/or agonist in the retina. Preferably, this treatment should be initiated prior to the acquisition of severe disease requiring photocoagulation.

[751] Within another aspect of the present invention, methods are provided for treating retrolental fibroplasia, comprising the step of administering to a patient a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist to the eye, such

that the formation of blood vessels is inhibited. The compound may be administered topically, via intravitreous injection and/or via intraocular implants.

[752] Additionally, disorders which can be treated with the polynucleotides, polypeptides, agonists and/or agonists include, but are not limited to, hemangioma, arthritis, psoriasis, angiofibroma, atherosclerotic plaques, delayed wound healing, granulations, hemophilic joints, hypertrophic scars, nonunion fractures, Osler-Weber syndrome, pyogenic granuloma, scleroderma, trachoma, and vascular adhesions.

[753] Moreover, disorders and/or states, which can be treated, prevented, diagnosed, and/or prognosed with the the polynucleotides, polypeptides, agonists and/or agonists of the invention include, but are not limited to, solid tumors, blood born tumors such as leukemias, tumor metastasis, Kaposi's sarcoma, benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas, rheumatoid arthritis, psoriasis, ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, and uvietis, delayed wound healing, endometriosis, vascluogenesis, granulations, hypertrophic scars (keloids), nonunion fractures, scleroderma, trachoma, vascular adhesions, myocardial angiogenesis, coronary collaterals, cerebral collaterals, arteriovenous malformations, ischemic limb angiogenesis, Osler-Webber Syndrome, plaque neovascularization, telangiectasia, hemophiliac joints, angiofibroma fibromuscular dysplasia, wound granulation, Crohn's disease, atherosclerosis, birth control agent by preventing vascularization required for embryo implantation controlling menstruation, diseases that have angiogenesis as a pathologic consequence such as cat scratch disease (Rochele minalia quintosa), ulcers (Helicobacter pylori), Bartonellosis and bacillary angiomatosis.

[754] In one aspect of the birth control method, an amount of the compound sufficient to block embryo implantation is administered before or after intercourse and fertilization have occurred, thus providing an effective method of birth control, possibly a "morning after" method. Polynucleotides, polypeptides, agonists and/or agonists may also be used in controlling menstruation or administered as either a peritoneal lavage fluid or for peritoneal implantation in the treatment of endometriosis.

[755] Polynucleotides, polypeptides, agonists and/or agonists of the present invention may be incorporated into surgical sutures in order to prevent stitch granulomas.

[756] Polynucleotides, polypeptides, agonists and/or agonists may be utilized in a wide variety of surgical procedures. For example, within one aspect of the present invention a compositions (in the form of, for example, a spray or film) may be utilized to coat or spray an area prior to removal of a tumor, in order to isolate normal surrounding tissues from malignant tissue, and/or to prevent the spread of disease to surrounding tissues. Within other aspects of the present invention, compositions (e.g., in the form of a spray) may be delivered via endoscopic procedures in order to coat tumors, or inhibit angiogenesis in a desired locale. Within yet other aspects of the present invention, surgical meshes which have been coated with anti- angiogenic compositions of the present invention may be utilized in any procedure wherein a surgical mesh might be utilized. For example, within one embodiment of the invention a surgical mesh laden with an anti-angiogenic composition may be utilized during abdominal cancer resection surgery (e.g., subsequent to colon resection) in order to provide support to the structure, and to release an amount of the anti-angiogenic factor.

[757] Within further aspects of the present invention, methods are provided for treating tumor excision sites, comprising administering a polynucleotide, polypeptide, agonist and/or agonist to the resection margins of a tumor subsequent to excision, such that the local recurrence of cancer and the formation of new blood vessels at the site is inhibited. Within one embodiment of the invention, the anti-angiogenic compound is administered directly to the tumor excision site (e.g., applied by swabbing, brushing or otherwise coating the resection margins of the tumor with the anti-angiogenic compound). Alternatively, the anti-angiogenic compounds may be incorporated into known surgical pastes prior to administration. Within particularly preferred embodiments of the invention, the anti-angiogenic compounds are applied after hepatic resections for malignancy, and after neurosurgical operations.

[758] Within one aspect of the present invention, polynucleotides, polypeptides, agonists and/or agonists may be administered to the resection margin of a wide variety of tumors, including for example, breast, colon, brain and hepatic tumors. For example, within one embodiment of the invention, anti-angiogenic compounds may be administered to the site of a neurological tumor subsequent to excision, such that the formation of new blood vessels at the site are inhibited.

[759] The polynucleotides, polypeptides, agonists and/or agonists of the present invention may also be administered along with other anti-angiogenic factors. Representative

examples of other anti-angiogenic factors include: Anti-Invasive Factor, retinoic acid and derivatives thereof, paclitaxel, Suramin, Tissue Inhibitor of Metalloproteinase-1, Tissue Inhibitor of Metalloproteinase-2, Plasminogen Activator Inhibitor-1, Plasminogen Activator Inhibitor-2, and various forms of the lighter "d group" transition metals.

[760] Lighter "d group" transition metals include, for example, vanadium, molybdenum, tungsten, titanium, niobium, and tantalum species. Such transition metal species may form transition metal complexes. Suitable complexes of the above-mentioned transition metal species include oxo transition metal complexes.

[761] Representative examples of vanadium complexes include oxo vanadium complexes such as vanadate and vanadyl complexes. Suitable vanadate complexes include metavanadate and orthovanadate complexes such as, for example, ammonium metavanadate, sodium metavanadate, and sodium orthovanadate. Suitable vanadyl complexes include, for example, vanadyl acetylacetonate and vanadyl sulfate including vanadyl sulfate hydrates such as vanadyl sulfate mono- and trihydrates.

[762] Representative examples of tungsten and molybdenum complexes also include oxo complexes. Suitable oxo tungsten complexes include tungstate and tungsten oxide complexes. Suitable tungstate complexes include ammonium tungstate, calcium tungstate, sodium tungstate dihydrate, and tungstic acid. Suitable tungsten oxides include tungsten (IV) oxide and tungsten (VI) oxide. Suitable oxo molybdenum complexes include molybdate, molybdenum oxide, and molybdenyl complexes. Suitable molybdate complexes include ammonium molybdate and its hydrates, sodium molybdate and its hydrates, and potassium molybdate and its hydrates. Suitable molybdenum oxides include molybdenum (VI) oxide, molybdenum (VI) oxide, and molybdic acid. Suitable molybdenyl complexes include, for example, molybdenyl acetylacetonate. Other suitable tungsten and molybdenum complexes include hydroxo derivatives derived from, for example, glycerol, tartaric acid, and sugars.

[763] A wide variety of other anti-angiogenic factors may also be utilized within the context of the present invention. Representative examples include platelet factor 4; protamine sulphate; sulphated chitin derivatives (prepared from queen crab shells), (Murata et al., Cancer Res. 51:22-26, 1991); Sulphated Polysaccharide Peptidoglycan Complex (SP- PG) (the function of this compound may be enhanced by the presence of steroids such as estrogen, and tamoxifen citrate); Staurosporine; modulators of matrix metabolism, including for example, proline analogs, cishydroxyproline, d,L-3,4-dehydroproline, Thiaproline,

alpha,alpha-dipyridyl, aminopropionitrile fumarate; 4-propyl-5-(4-pyridinyl)-2(3H)-oxazolone; Methotrexate; Mitoxantrone; Heparin; Interferons; 2 Macroglobulin-serum; ChIMP-3 (Pavloff et al., J. Bio. Chem. 267:17321-17326, 1992); Chymostatin (Tomkinson et al., Biochem J. 286:475-480, 1992); Cyclodextrin Tetradecasulfate; Eponemycin; Camptothecin; Fumagillin (Ingber et al., Nature 348:555-557, 1990); Gold Sodium Thiomalate ("GST"; Matsubara and Ziff, J. Clin. Invest. 79:1440-1446, 1987); anticollagenase-serum; alpha2-antiplasmin (Holmes et al., J. Biol. Chem. 262(4):1659-1664, 1987); Bisantrene (National Cancer Institute); Lobenzarit disodium (N-(2)-carboxyphenyl-4-chloroanthronilic acid disodium or "CCA"; Takeuchi et al., Agents Actions 36:312-316, 1992); Thalidomide; Angostatic steroid; AGM-1470; carboxynaminolmidazole; and metalloproteinase inhibitors such as BB94.

Diseases at the Cellular Level

[764] Diseases associated with increased cell survival or the inhibition of apoptosis that could be treated, prevented, diagnosed, and/or prognosed using polynucleotides or polypeptides, as well as antagonists or agonists of the present invention, include cancers (such as follicular lymphomas, carcinomas with p53 mutations, and hormone-dependent tumors, including, but not limited to colon cancer, cardiac tumors, pancreatic cancer, melanoma, retinoblastoma, glioblastoma, lung cancer, intestinal cancer, testicular cancer, stomach cancer, neuroblastoma, myxoma, myoma, lymphoma, endothelioma, osteoblastoma, osteoclastoma, osteosarcoma, chondrosarcoma, adenoma, breast cancer, prostate cancer, Kaposi's sarcoma and ovarian cancer); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) and viral infections (such as herpes viruses, pox viruses and adenoviruses), inflammation, graft v. host disease, acute graft rejection, and chronic graft rejection.

[765] In preferred embodiments, polynucleotides, polypeptides, and/or antagonists of the invention are used to inhibit growth, progression, and/or metasis of cancers, in particular those listed above.

[766] Additional diseases or conditions associated with increased cell survival that could be treated or detected by polynucleotides or polypeptides, or agonists or antagonists of the

present invention include, but are not limited to, progression, and/or metastases of malignancies and related disorders such as leukemia (including acute leukemias (e.g., acute lymphocytic leukemia, acute myelocytic leukemia (including myeloblastic, promyelocytic, myelomonocytic, monocytic, and erythroleukemia)) and chronic leukemias (e.g., chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia)), polycythemia vera, lymphomas (e.g., Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, and solid tumors including, but not limited to, sarcomas and carcinomas such as fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, menangioma, melanoma, neuroblastoma, and retinoblastoma.

[767] Diseases associated with increased apoptosis that could be treated, prevented, diagnosed, and/or prognesed using polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, include, but are not limited to, AIDS; neurodegenerative disorders (such as Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis, Retinitis pigmentosa, Cerebellar degeneration and brain tumor or prior associated disease); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) myelodysplastic syndromes (such as aplastic anemia), graft v. host disease, ischemic injury (such as that caused by myocardial infarction, stroke and reperfusion injury), liver injury (e.g., hepatitis related liver injury, ischemia/reperfusion injury, cholestosis (bile duct injury)

and liver cancer); toxin-induced liver disease (such as that caused by alcohol), septic shock, cachexia and anorexia.

Wound Healing and Epithelial Cell Proliferation

[768] In accordance with yet a further aspect of the present invention, there is provided a process for utilizing polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, for therapeutic purposes, for example, to stimulate epithelial cell proliferation and basal keratinocytes for the purpose of wound healing, and to stimulate hair follicle production and healing of dermal wounds. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may be clinically useful in stimulating wound healing including surgical wounds, excisional wounds, deep wounds involving damage of the dermis and epidermis, eye tissue wounds, dental tissue wounds, oral cavity wounds, diabetic ulcers, dermal ulcers, cubitus ulcers, arterial ulcers, venous stasis ulcers, burns resulting from heat exposure or chemicals, and other abnormal wound healing conditions such as uremia, malnutrition, vitamin deficiencies and complications associated with systemic treatment with steroids, radiation therapy and antineoplastic drugs and antimetabolites. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to promote dermal reestablishment subsequent to dermal loss

[769] Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to increase the adherence of skin grafts to a wound bed and to stimulate re-epithelialization from the wound bed. The following are types of grafts that polynucleotides or polypeptides, agonists or antagonists of the present invention, could be used to increase adherence to a wound bed: autografts, artificial skin, allografts, autodermic graft, autoepdermic grafts, avacular grafts, Blair-Brown grafts, bone graft, brephoplastic grafts, cutis graft, delayed graft, dermic graft, epidermic graft, fascia graft, full thickness graft, heterologous graft, xenograft, homologous graft, hyperplastic graft, lamellar graft, mesh graft, mucosal graft, Ollier-Thiersch graft, omenpal graft, patch graft, pedicle graft, penetrating graft, split skin graft, thick split graft. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, can be used to promote skin strength and to improve the appearance of aged skin.

[770] It is believed that polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, will also produce changes in hepatocyte proliferation, and epithelial cell proliferation in the lung, breast, pancreas, stomach, small intestine, and large intestine. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could promote proliferation of epithelial cells such as sebocytes, hair follicles, hepatocytes, type II pneumocytes, mucin-producing goblet cells, and other epithelial cells and their progenitors contained within the skin, lung, liver, and gastrointestinal tract. Polynucleotides or polypeptides, agonists or antagonists of the present invention, may promote proliferation of endothelial cells, keratinocytes, and basal keratinocytes.

[771] Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could also be used to reduce the side effects of gut toxicity that result from radiation, chemotherapy treatments or viral infections. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may have a cytoprotective effect on the small intestine mucosa. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may also stimulate healing of mucositis (mouth ulcers) that result from chemotherapy and viral infections.

[772] Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could further be used in full regeneration of skin in full and partial thickness skin defects, including burns, (i.e., repopulation of hair follicles, sweat glands, and sebaceous glands), treatment of other skin defects such as psoriasis. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to treat epidermolysis bullosa, a defect in adherence of the epidermis to the underlying dermis which results in frequent, open and painful blisters by accelerating reepithelialization of these lesions. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could also be used to treat gastric and doudenal ulcers and help heal by scar formation of the mucosal lining and regeneration of glandular mucosa and duodenal mucosal lining more rapidly. Inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis, are diseases which result in destruction of the mucosal surface of the small or large intestine, respectively. Thus, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to promote the resurfacing of the mucosal surface to aid more rapid healing and to prevent progression of inflammatory bowel disease. Treatment with polynucleotides or polypeptides, agonists or antagonists of the present invention, is

expected to have a significant effect on the production of mucus throughout the gastrointestinal tract and could be used to protect the intestinal mucosa from injurious substances that are ingested or following surgery. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to treat diseases associate with the under expression.

[773] Moreover, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to prevent and heal damage to the lungs due to various pathological states. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, which could stimulate proliferation and differentiation and promote the repair of alveoli and brochiolar epithelium to prevent or treat acute or chronic lung damage. For example, emphysema, which results in the progressive loss of aveoli, and inhalation injuries, i.e., resulting from smoke inhalation and burns, that cause necrosis of the bronchiolar epithelium and alveoli could be effectively treated using polynucleotides or polypeptides, agonists or antagonists of the present invention. Also, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to stimulate the proliferation of and differentiation of type II pneumocytes, which may help treat or prevent disease such as hyaline membrane diseases, such as infant respiratory distress syndrome and bronchopulmonary displasia, in premature infants.

[774] Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could stimulate the proliferation and differentiation of hepatocytes and, thus, could be used to alleviate or treat liver diseases and pathologies such as fulminant liver failure caused by cirrhosis, liver damage caused by viral hepatitis and toxic substances (i.e., acetaminophen, carbon tetraholoride and other hepatotoxins known in the art).

[775] In addition, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used treat or prevent the onset of diabetes mellitus. In patients with newly diagnosed Types I and II diabetes, where some islet cell function remains, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to maintain the islet function so as to alleviate, delay or prevent permanent manifestation of the disease. Also, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used as an auxiliary in islet cell transplantation to improve or promote islet cell function.

Neural Activity and Neurological Diseases

[776] The polynucleotides, polypeptides and agonists or antagonists of the invention may be used for the diagnosis and/or treatment of diseases, disorders, damage or injury of the brain and/or nervous system. Nervous system disorders that can be treated with the compositions of the invention (e.g., polypeptides, polynucleotides, and/or agonists or antagonists), include, but are not limited to, nervous system injuries, and diseases or disorders which result in either a disconnection of axons, a diminution or degeneration of neurons, or demyelination. Nervous system lesions which may be treated in a patient (including human and non-human mammalian patients) according to the methods of the invention, include but are not limited to, the following lesions of either the central (including spinal cord, brain) or peripheral nervous systems: (1) ischemic lesions, in which a lack of oxygen in a portion of the nervous system results in neuronal injury or death, including cerebral infarction or ischemia, or spinal cord infarction or ischemia; (2) traumatic lesions, including lesions caused by physical injury or associated with surgery, for example, lesions which sever a portion of the nervous system, or compression injuries; (3) malignant lesions, in which a portion of the nervous system is destroyed or injured by malignant tissue which is either a nervous system associated malignancy or a malignancy derived from non-nervous system tissue; (4) infectious lesions, in which a portion of the nervous system is destroyed or injured as a result of infection, for example, by an abscess or associated with infection by human immunodeficiency virus, herpes zoster, or herpes simplex virus or with Lyme disease, tuberculosis, or syphilis; (5) degenerative lesions, in which a portion of the nervous system is destroyed or injured as a result of a degenerative process including but not limited to, degeneration associated with Parkinson's disease, Alzheimer's disease, Huntington's chorea, or amyotrophic lateral sclerosis (ALS); (6) lesions associated with nutritional diseases or disorders, in which a portion of the nervous system is destroyed or injured by a nutritional disorder or disorder of metabolism including, but not limited to, vitamin B12 deficiency, folic acid deficiency, Wernicke disease, tobacco-alcohol amblyopia, Marchiafava-Bignami disease (primary degeneration of the corpus callosum), and alcoholic cerebellar degeneration; (7) neurological lesions associated with systemic diseases including, but not limited to, diabetes (diabetic neuropathy, Bell's palsy), systemic lupus erythematosus, carcinoma, or sarcoidosis; (8) lesions caused by toxic substances including alcohol, lead, or particular neurotoxins; and (9) demyelinated lesions in which a portion of the nervous system is destroyed or injured by

a demyelinating disease including, but not limited to, multiple sclerosis, human immunodeficiency virus-associated myelopathy, transverse myelopathy or various etiologies, progressive multifocal leukoencephalopathy, and central pontine myelinolysis.

[777] In one embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to protect neural cells from the damaging effects of hypoxia. In a further preferred embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to protect neural cells from the damaging effects of cerebral hypoxia. According to this embodiment, the compositions of the invention are used to treat or prevent neural cell injury associated with cerebral hypoxia. In one non-exclusive aspect of this embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention, are used to treat or prevent neural cell injury associated with cerebral ischemia. In another non-exclusive aspect of this embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent neural cell injury associated with cerebral infarction.

[778] In another preferred embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent neural cell injury associated with a stroke. In a specific embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent cerebral neural cell injury associated with a stroke.

[779] In another preferred embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent neural cell injury associated with a heart attack. In a specific embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent cerebral neural cell injury associated with a heart attack.

[780] The compositions of the invention which are useful for treating or preventing a nervous system disorder may be selected by testing for biological activity in promoting the survival or differentiation of neurons. For example, and not by way of limitation, compositions of the invention which elicit any of the following effects may be useful according to the invention: (1) increased survival time of neurons in culture either in the presence or absence of hypoxia or hypoxic conditions; (2) increased sprouting of neurons in culture or *in vivo*; (3) increased production of a neuron-associated molecule in culture or *in vivo*, *e.g.*, choline acetyltransferase or acetylcholinesterase with respect to motor neurons; or

(4) decreased symptoms of neuron dysfunction *in vivo*. Such effects may be measured by any method known in the art. In preferred, non-limiting embodiments, increased survival of neurons may routinely be measured using a method set forth herein or otherwise known in the art, such as, for example, in Zhang *et al., Proc Natl Acad Sci USA* 97:3637-42 (2000) or in Arakawa *et al., J. Neurosci., 10*:3507-15 (1990); increased sprouting of neurons may be detected by methods known in the art, such as, for example, the methods set forth in Pestronk *et al., Exp. Neurol., 70*:65-82 (1980), or Brown *et al., Ann. Rev. Neurosci., 4*:17-42 (1981); increased production of neuron-associated molecules may be measured by bioassay, enzymatic assay, antibody binding, Northern blot assay, etc., using techniques known in the art and depending on the molecule to be measured; and motor neuron dysfunction may be measured by assessing the physical manifestation of motor neuron disorder, e.g., weakness, motor neuron conduction velocity, or functional disability.

[781] In specific embodiments, motor neuron disorders that may be treated according to the invention include, but are not limited to, disorders such as infarction, infection, exposure to toxin, trauma, surgical damage, degenerative disease or malignancy that may affect motor neurons as well as other components of the nervous system, as well as disorders that selectively affect neurons such as amyotrophic lateral sclerosis, and including, but not limited to, progressive spinal muscular atrophy, progressive bulbar palsy, primary lateral sclerosis, infantile and juvenile muscular atrophy, progressive bulbar paralysis of childhood (Fazio-Londe syndrome), poliomyelitis and the post polio syndrome, and Hereditary Motorsensory Neuropathy (Charcot-Marie-Tooth Disease).

[782] Further, polypeptides or polynucleotides of the invention may play a role in neuronal survival; synapse formation; conductance; neural differentiation, etc. Thus, compositions of the invention (including polynucleotides, polypeptides, and agonists or antagonists) may be used to diagnose and/or treat or prevent diseases or disorders associated with these roles, including, but not limited to, learning and/or cognition disorders. The compositions of the invention may also be useful in the treatment or prevention of neurodegenerative disease states and/or behavioural disorders. Such neurodegenerative disease states and/or behavioral disorders include, but are not limited to, Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding,

sleep patterns, balance, and perception. In addition, compositions of the invention may also play a role in the treatment, prevention and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders.

[783] Additionally, polypeptides, polynucleotides and/or agonists or antagonists of the invention, may be useful in protecting neural cells from diseases, damage, disorders, or injury, associated with cerebrovascular disorders including, but not limited to, carotid artery diseases (e.g., carotid artery thrombosis, carotid stenosis, or Moyamoya Disease), cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformations, cerebral artery diseases, cerebral embolism and thrombosis (e.g., carotid artery thrombosis, sinus thrombosis, or Wallenberg's Syndrome), cerebral hemorrhage (e.g., epidural or subdural hematoma, or subarachnoid hemorrhage), cerebral infarction, cerebral ischemia (e.g., transient cerebral ischemia, Subclavian Steal Syndrome, or vertebrobasilar insufficiency), vascular dementia (e.g., multi-infarct), leukomalacia, periventricular, and vascular headache (e.g., cluster headache or migraines).

[784] In accordance with yet a further aspect of the present invention, there is provided a process for utilizing polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, for therapeutic purposes, for example, to stimulate neurological cell proliferation and/or differentiation. Therefore, polynucleotides, polypeptides, agonists and/or antagonists of the invention may be used to treat and/or detect neurologic diseases. Moreover, polynucleotides or polypeptides, or agonists or antagonists of the invention, can be used as a marker or detector of a particular nervous system disease or disorder.

[785] Examples of neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include brain diseases, such as metabolic brain diseases which includes phenylketonuria such as maternal phenylketonuria, pyruvate carboxylase deficiency, pyruvate dehydrogenase complex deficiency, Wernicke's Encephalopathy, brain edema, brain neoplasms such as cerebellar neoplasms which include infratentorial neoplasms, cerebral ventricle neoplasms such as choroid plexus neoplasms, hypothalamic neoplasms, supratentorial neoplasms, canavan disease, cerebellar diseases such as cerebellar ataxia which include spinocerebellar degeneration such as ataxia telangiectasia, cerebellar dyssynergia, Friederich's Ataxia, Machado-Joseph Disease, olivopontocerebellar atrophy, cerebellar neoplasms such as

infratentorial neoplasms, diffuse cerebral sclerosis such as encephalitis periaxialis, globoid cell leukodystrophy, metachromatic leukodystrophy and subacute sclerosing panencephalitis.

[786] Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include cerebrovascular disorders (such as carotid artery diseases which include carotid artery thrombosis, carotid stenosis and Moyamoya Disease), cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformations, cerebral artery diseases, cerebral embolism and thrombosis such as carotid artery thrombosis, sinus thrombosis and Wallenberg's Syndrome, cerebral hemorrhage such as epidural hematoma, subdural hematoma and subarachnoid hemorrhage, cerebral infarction, cerebral ischemia such as transient cerebral ischemia, Subclavian Steal Syndrome and vertebrobasilar insufficiency, vascular dementia such as multi-infarct dementia, periventricular leukomalacia, vascular headache such as cluster headache and migraine.

[787] Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include dementia such as AIDS Dementia Complex, presenile dementia such as Alzheimer's Disease and Creutzfeldt-Jakob Syndrome, senile dementia such as Alzheimer's Disease and progressive supranuclear palsy, vascular dementia such as multi-infarct dementia, encephalitis which include encephalitis periaxialis, viral encephalitis such as epidemic encephalitis, Japanese Encephalitis, St. Louis Encephalitis, tick-borne encephalitis and West Nile Fever, acute disseminated encephalomyelitis, meningoencephalitis such as uveomeningoencephalitic syndrome, Postencephalitic Parkinson Disease and subacute sclerosing panencephalitis, encephalomalacia such as periventricular leukomalacia, epilepsy such as generalized epilepsy which includes infantile spasms, absence epilepsy, myoclonic epilepsy which includes MERRF Syndrome, tonic-clonic epilepsy, partial epilepsy such as complex partial epilepsy, frontal lobe epilepsy and temporal lobe epilepsy, post-traumatic epilepsy, status epilepticus such as Epilepsia Partialis Continua, and Hallervorden-Spatz Syndrome.

[788] Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include hydrocephalus such as Dandy-Walker Syndrome and normal pressure hydrocephalus, hypothalamic diseases such as hypothalamic neoplasms, cerebral malaria, narcolepsy which

includes cataplexy, bulbar poliomyelitis, cerebri pseudotumor, Rett Syndrome, Reye's Syndrome, thalamic diseases, cerebral toxoplasmosis, intracranial tuberculoma and Zellweger Syndrome, central nervous system infections such as AIDS Dementia Complex, Brain Abscess, subdural empyema, encephalomyelitis such as Equine Encephalomyelitis, Venezuelan Equine Encephalomyelitis, Necrotizing Hemorrhagic Encephalomyelitis, Visna, and cerebral malaria.

[789] Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include meningitis such as arachnoiditis, aseptic meningtitis such as viral meningtitis which includes lymphocytic choriomeningitis, Bacterial meningtitis which includes Haemophilus Meningtitis, Listeria Meningtitis, Meningococcal Meningtitis such as Waterhouse-Friderichsen Syndrome, Pneumococcal Meningtitis and meningeal tuberculosis, fungal meningitis such as Cryptococcal Meningtitis, subdural effusion, meningoencephalitis such as uvemeningoencephalitic syndrome, myelitis such as transverse myelitis, neurosyphilis such as tabes dorsalis, poliomyelitis which includes bulbar poliomyelitis and postpoliomyelitis syndrome, prion diseases (such as Creutzfeldt-Jakob Syndrome, Bovine Spongiform Encephalopathy, Gerstmann-Straussler Syndrome, Kuru, Scrapie), and cerebral toxoplasmosis.

[790] Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include central nervous system neoplasms such as brain neoplasms that include cerebellar neoplasms such as infratentorial neoplasms, cerebral ventricle neoplasms such as choroid plexus neoplasms, hypothalamic neoplasms and supratentorial neoplasms, meningeal neoplasms, spinal cord neoplasms which include epidural neoplasms, demyelinating diseases such as Canavan Diseases, diffuse cerebral sceloris which includes adrenoleukodystrophy, encephalitis periaxialis, globoid cell leukodystrophy, diffuse cerebral sclerosis such as metachromatic leukodystrophy, allergic encephalomyelitis, necrotizing hemorrhagic encephalomyelitis, progressive multifocal leukoencephalopathy, multiple sclerosis, central pontine myelinolysis, transverse myelitis, neuromyelitis optica, Scrapie, Swayback, Chronic Fatigue Syndrome, Visna, High Pressure Nervous Syndrome, Meningism, spinal cord diseases such as amyotonia congenita, amyotrophic lateral sclerosis, spinal muscular atrophy such as Werdnig-Hoffmann Disease, spinal cord compression, spinal cord neoplasms such as

epidural neoplasms, syringomyelia, Tabes Dorsalis, Stiff-Man Syndrome, mental retardation such as Angelman Syndrome, Cri-du-Chat Syndrome, De Lange's Syndrome, Down Syndrome, Gangliosidoses such as gangliosidoses G(M1), Sandhoff Disease, Tay-Sachs Disease, Hartnup Disease, homocystinuria, Laurence-Moon- Biedl Syndrome, Lesch-Nyhan Syndrome, Maple Syrup Urine Disease, mucolipidosis such as fucosidosis, neuronal ceroid-lipofuscinosis, oculocerebrorenal syndrome, phenylketonuria such as maternal phenylketonuria, Prader-Willi Syndrome, Rett Syndrome, Rubinstein-Taybi Syndrome, Tuberous Sclerosis, WAGR Syndrome, nervous system abnormalities such as holoprosencephaly, neural tube defects such as anencephaly which includes hydrangencephaly, Arnold-Chairi Deformity, encephalocele, meningocele, meningomyelocele, spinal dysraphism such as spina bifida cystica and spina bifida occulta.

[791] Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include hereditary motor and sensory neuropathies which include Charcot-Marie Disease, Hereditary optic atrophy, Refsum's Disease, hereditary spastic paraplegia, Werdnig-Hoffmann Disease, Hereditary Sensory and Autonomic Neuropathies such as Congenital Analgesia and Familial Dysautonomia, Neurologic manifestations (such as agnosia that include Gerstmann's Syndrome, Amnesia such as retrograde amnesia, apraxia, neurogenic bladder, cataplexy, communicative disorders such as hearing disorders that includes deafness, partial hearing loss, loudness recruitment and tinnitus, language disorders such as aphasia which include agraphia, anomia, broca aphasia, and Wernicke Aphasia, Dyslexia such as Acquired Dyslexia, language development disorders, speech disorders such as aphasia which includes anomia, broca aphasia and Wernicke Aphasia, articulation disorders, communicative disorders such as speech disorders which include dysarthria, echolalia, mutism and stuttering, voice disorders such as aphonia and hoarseness, decerebrate state, delirium, fasciculation, hallucinations, meningism, movement disorders such as angelman syndrome, ataxia, athetosis, chorea, dystonia, hypokinesia, muscle hypotonia, myoclonus, tic, torticollis and tremor, muscle hypertonia such as muscle rigidity such as stiff-man syndrome, muscle spasticity, paralysis such as facial paralysis which includes Herpes Zoster Oticus, Gastroparesis, Hemiplegia, ophthalmoplegia such as diplopia, Duane's Syndrome, Horner's Syndrome, Chronic progressive external ophthalmoplegia such as Kearns Syndrome, Bulbar Paralysis, Tropical Spastic Paraparesis, Paraplegia such as Brown-Sequard Syndrome,

quadriplegia, respiratory paralysis and vocal cord paralysis, paresis, phantom limb, taste disorders such as ageusia and dysgeusia, vision disorders such as amblyopia, blindness, color vision defects, diplopia, hemianopsia, scotoma and subnormal vision, sleep disorders such as hypersomnia which includes Kleine-Levin Syndrome, insomnia, and somnambulism, spasm such as trismus, unconsciousness such as coma, persistent vegetative state and syncope and vertigo, neuromuscular diseases such as amyotonia congenita, amyotrophic lateral sclerosis, Lambert-Eaton Myasthenic Syndrome, motor neuron disease, muscular atrophy such as spinal muscular atrophy, Charcot-Marie Disease and Werdnig-Hoffmann Disease, Postpoliomyelitis Syndrome, Muscular Dystrophy, Myasthenia Gravis, Myotonia Atrophica, Myotonia Confenita, Nemaline Myopathy, Familial Periodic Paralysis, Multiplex Paramyloclonus, Tropical Spastic Paraparesis and Stiff-Man Syndrome, peripheral nervous system diseases such as acrodynia, amyloid neuropathies, autonomic nervous system diseases such as Adie's Syndrome, Barre-Lieou Syndrome, Familial Dysautonomia, Horner's Syndrome, Reflex Sympathetic Dystrophy and Shy-Drager Syndrome, Cranial Nerve Diseases such as Acoustic Nerve Diseases such as Acoustic Neuroma which includes Neurofibromatosis 2, Facial Nerve Diseases such as Facial Neuralgia,Melkersson-Rosenthal Syndrome, ocular motility disorders which includes amblyopia, nystagmus, oculomotor nerve paralysis, ophthalmoplegia such as Duane's Syndrome, Horner's Syndrome, Chronic Progressive External Ophthalmoplegia which includes Kearns Syndrome, Strabismus such as Esotropia and Exotropia, Oculomotor Nerve Paralysis, Optic Nerve Diseases such as Optic Atrophy which includes Hereditary Optic Atrophy, Optic Disk Drusen, Optic Neuritis such as Neuromyelitis Optica, Papilledema, Trigeminal Neuralgia, Vocal Cord Paralysis, Demyelinating Diseases such as Neuromyelitis Optica and Swayback, and Diabetic neuropathies such as diabetic foot.

[792] Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include nerve compression syndromes such as carpal tunnel syndrome, tarsal tunnel syndrome, thoracic outlet syndrome such as cervical rib syndrome, ulnar nerve compression syndrome, neuralgia such as causalgia, cervico-brachial neuralgia, facial neuralgia and trigeminal neuralgia, neuritis such as experimental allergic neuritis, optic neuritis, polyneuritis, polyradiculoneuritis and radiculities such as polyradiculitis, hereditary motor and sensory neuropathies such as Charcot-Marie Disease, Hereditary Optic Atrophy, Refsum's Disease,

Hereditary Spastic Paraplegia and Werdnig-Hoffmann Disease, Hereditary Sensory and Autonomic Neuropathies which include Congenital Analgesia and Familial Dysautonomia, POEMS Syndrome, Sciatica, Gustatory Sweating and Tetany).

Endocrine Disorders

[793] Polynucleotides or polypeptides, or agonists or antagonists of the present invention, may be used to treat, prevent, diagnose, and/or prognose disorders and/or diseases related to hormone imbalance, and/or disorders or diseases of the endocrine system.

[794] Hormones secreted by the glands of the endocrine system control physical growth, sexual function, metabolism, and other functions. Disorders may be classified in two ways: disturbances in the production of hormones, and the inability of tissues to respond to hormones. The etiology of these hormone imbalance or endocrine system diseases, disorders or conditions may be genetic, somatic, such as cancer and some autoimmune diseases, acquired (e.g., by chemotherapy, injury or toxins), or infectious. Moreover, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention can be used as a marker or detector of a particular disease or disorder related to the endocrine system and/or hormone imbalance.

[795] Endocrine system and/or hormone imbalance and/or diseases encompass disorders of uterine motility including, but not limited to: complications with pregnancy and labor (e.g., pre-term labor, post-term pregnancy, spontaneous abortion, and slow or stopped labor); and disorders and/or diseases of the menstrual cycle (e.g., dysmenorrhea and endometriosis).

[796] Endocrine system and/or hormone imbalance disorders and/or diseases include disorders and/or diseases of the pancreas, such as, for example, diabetes mellitus, diabetes insipidus, congenital pancreatic agenesis, pheochromocytoma--islet cell tumor syndrome; disorders and/or diseases of the adrenal glands such as, for example, Addison's Disease, corticosteroid deficiency, virilizing disease, hirsutism, Cushing's Syndrome, hyperaldosteronism, pheochromocytoma; disorders and/or diseases of the pituitary gland, such as, for example, hyperpituitarism, hypopituitarism, pituitary dwarfism, pituitary adenoma, panhypopituitarism, acromegaly, gigantism; disorders and/or diseases of the thyroid, including but not limited to, hyperthyroidism, hypothyroidism, Plummer's disease, Graves' disease (toxic diffuse goiter), toxic nodular goiter, thyroiditis (Hashimoto's

thyroiditis, subacute granulomatous thyroiditis, and silent lymphocytic thyroiditis), Pendred's syndrome, myxedema, cretinism, thyrotoxicosis, thyroid hormone coupling defect, thymic aplasia, Hurthle cell tumours of the thyroid, thyroid cancer, thyroid carcinoma, Medullary thyroid carcinoma; disorders and/or diseases of the parathyroid, such as, for example, hyperparathyroidism, hypoparathyroidism; disorders and/or diseases of the hypothalamus.

[797] In specific embodiments, the polynucleotides and/or polypeptides corresponding to this gene and/or agonists or antagonists of those polypeptides (including antibodies) as well as fragments and variants of those polynucleotides, polypeptides, agonists and antagonists, may be used to diagnose, prognose, treat, prevent, or ameliorate diseases and disorders associated with aberrant glucose metabolism or glucose uptake into cells.

[798] In a specific embodiment, the polynucleotides and/or polypeptides corresponding to this gene and/or agonists and/or antagonists thereof may be used to diagnose, prognose, treat, prevent, and/or ameliorate type I diabetes mellitus (insulin dependent diabetes mellitus, IDDM).

[799] In another embodiment, the polynucleotides and/or polypeptides corresponding to this gene and/or agonists and/or antagonists thereof may be used to diagnose, prognose, treat, prevent, and/or ameliorate type II diabetes mellitus (insulin resistant diabetes mellitus).

[800] Additionally, in other embodiments, the polynucleotides and/or polypeptides corresponding to this gene and/or antagonists thereof (especially neutralizing or antagonistic antibodies) may be used to diagnose, prognose, treat, prevent, or ameliorate conditions associated with (type I or type II) diabetes mellitus, including, but not limited to, diabetic ketoacidosis, diabetic coma, nonketotic hyperglycemic-hyperosmolar coma, seizures, mental confusion, drowsiness, cardiovascular disease (e.g., heart disease, atherosclerosis, microvascular disease, hypertension, stroke, and other diseases and disorders as described in the "Cardiovascular Disorders" section), dyslipidemia, kidney disease (e.g., renal failure, nephropathy other diseases and disorders as described in the "Renal Disorders" section), nerve damage, neuropathy, vision impairment (e.g., diabetic retinopathy and blindness), ulcers and impaired wound healing, infections (e.g., infectious diseases and disorders as described in the "Infectious Diseases" section, especially of the urinary tract and skin), carpal tunnel syndrome and Dupuytren's contracture.

[801] In other embodiments, the polynucleotides and/or polypeptides corresponding to this gene and/or agonists or antagonists thereof are administered to an animal, preferably a

mammal, and most preferably a human, in order to regulate the animal's weight. In specific embodiments the polynucleotides and/or polypeptides corresponding to this gene and/or agonists or antagonists thereof are administered to an animal, preferably a mammal, and most preferably a human, in order to control the animal's weight by modulating a biochemical pathway involving insulin. In still other embodiments the polynucleotides and/or polypeptides corresponding to this gene and/or agonists or antagonists thereof are administered to an animal, preferably a mammal, and most preferably a human, in order to control the animal's weight by modulating a biochemical pathway involving insulin-like growth factor.

[802] In addition, endocrine system and/or hormone imbalance disorders and/or diseases may also include disorders and/or diseases of the testes or ovaries, including cancer. Other disorders and/or diseases of the testes or ovaries further include, for example, ovarian cancer, polycystic ovary syndrome, Klinefelter's syndrome, vanishing testes syndrome (bilateral anorchia), congenital absence of Leydig's cells, cryptorchidism, Noonan's syndrome, myotonic dystrophy, capillary haemangioma of the testis (benign), neoplasias of the testis and neo-testis.

[803] Moreover, endocrine system and/or hormone imbalance disorders and/or diseases may also include disorders and/or diseases such as, for example, polyglandular deficiency syndromes, pheochromocytoma, neuroblastoma, multiple Endocrine neoplasia, and disorders and/or cancers of endocrine tissues.

[804] In another embodiment, a polypeptide of the invention, or polynucleotides, antibodies, agonists, or antagonists corresponding to that polypeptide, may be used to diagnose, prognose, prevent, and/or treat endocrine diseases and/or disorders associated with the tissue(s) in which the polypeptide of the invention is expressed, including one, two, three, four, five, or more tissues disclosed in Table 10, column 2 (Library Code).

Reproductive System Disorders

[805] The polynucleotides or polypeptides, or agonists or antagonists of the invention may be used for the diagnosis, treatment, or prevention of diseases and/or disorders of the reproductive system. Reproductive system disorders that can be treated by the compositions of the invention, include, but are not limited to, reproductive system injuries, infections,

neoplastic disorders, congenital defects, and diseases or disorders which result in infertility, complications with pregnancy, labor, or parturition, and postpartum difficulties.

[806] Reproductive system disorders and/or diseases include diseases and/or disorders of the testes, including testicular atrophy, testicular feminization, cryptorchism (unilateral and bilateral), anorchia, ectopic testis, epididymitis and orchitis (typically resulting from infections such as, for example, gonorrhea, mumps, tuberculosis, and syphilis), testicular torsion, vasitis nodosa, germ cell tumors (e.g., seminomas, embryonal cell carcinomas, teratocarcinomas, choriocarcinomas, yolk sac tumors, and teratomas), stromal tumors (e.g., Leydig cell tumors), hydrocele, hematocele, varicocele, spermatocele, inguinal hernia, and disorders of sperm production (e.g., immotile cilia syndrome, aspermia, asthenozoospermia, azoospermia, oligospermia, and teratozoospermia).

[807] Reproductive system disorders also include disorders of the prostate gland, such as acute non-bacterial prostatitis, chronic non-bacterial prostatitis, acute bacterial prostatitis, chronic bacterial prostatitis, prostatodystonia, prostatosis, granulomatous prostatitis, malacoplakia, benign prostatic hypertrophy or hyperplasia, and prostate neoplastic disorders, including adenocarcinomas, transitional cell carcinomas, ductal carcinomas, and squamous cell carcinomas.

[808] Additionally, the compositions of the invention may be useful in the diagnosis, treatment, and/or prevention of disorders or diseases of the penis and urethra, including inflammatory disorders, such as balanoposthitis, balanitis xerotica obliterans, phimosis, paraphimosis, syphilis, herpes simplex virus, gonorrhea, non-gonococcal urethritis, chlamydia, mycoplasma, trichomonas, HIV, AIDS, Reiter's syndrome, condyloma acuminatum, condyloma latum, and pearly penile papules; urethral abnormalities, such as hypospadias, epispadias, and phimosis; premalignant lesions, including Erythroplasia of Queyrat, Bowen's disease, Bowenoid paplosis, giant condyloma of Buscke-Lowenstein, and varrucous carcinoma; penile cancers, including squamous cell carcinomas, carcinoma in situ, verrucous carcinoma, and disseminated penile carcinoma; urethral neoplastic disorders, including penile urethral carcinoma, bulbomembranous urethral carcinoma, and prostatic urethral carcinoma; and erectile disorders, such as priapism, Peyronie's disease, erectile dysfunction, and impotence.

[809] Moreover, diseases and/or disorders of the vas deferens include vasculititis and CBAVD (congenital bilateral absence of the vas deferens); additionally, the polynucleotides,

polypeptides, and agonists or antagonists of the present invention may be used in the diagnosis, treatment, and/or prevention of diseases and/or disorders of the seminal vesicles, including hydatid disease, congenital chloride diarrhea, and polycystic kidney disease.

[810] Other disorders and/or diseases of the male reproductive system include, for example, Klinefelter's syndrome, Young's syndrome, premature ejaculation, diabetes mellitus, cystic fibrosis, Kartagener's syndrome, high fever, multiple sclerosis, and gynecomastia.

[811] Further, the polynucleotides, polypeptides, and agonists or antagonists of the present invention may be used in the diagnosis, treatment, and/or prevention of diseases and/or disorders of the vagina and vulva, including bacterial vaginosis, candida vaginitis, herpes simplex virus, chancroid, granuloma inguinale, lymphogranuloma venereum, scabies, human papillomavirus, vaginal trauma, vulvar trauma, adenosis, chlamydia vaginitis, gonorrhea, trichomonas vaginitis, condyloma acuminatum, syphilis, molluscum contagiosum, atrophic vaginitis, Paget's disease, lichen sclerosus, lichen planus, vulvodynia, toxic shock syndrome, vaginismus, vulvovaginitis, vulvar vestibulitis, and neoplastic disorders, such as squamous cell hyperplasia, clear cell carcinoma, basal cell carcinoma, melanomas, cancer of Bartholin's gland, and vulvar intraepithelial neoplasia.

[812] Disorders and/or diseases of the uterus include dysmenorrhea, retroverted uterus, endometriosis, fibroids, adenomyosis, anovulatory bleeding, amenorrhea, Cushing's syndrome, hydatidiform moles, Asherman's syndrome, premature menopause, precocious puberty, uterine polyps, dysfunctional uterine bleeding (e.g., due to aberrant hormonal signals), and neoplastic disorders, such as adenocarcinomas, keiomyosarcomas, and sarcomas. Additionally, the polypeptides, polynucleotides, or agonists or antagonists of the invention may be useful as a marker or detector of, as well as in the diagnosis, treatment, and/or prevention of congenital uterine abnormalities, such as bicornuate uterus, septate uterus, simple unicornuate uterus, unicornuate uterus with a noncavitary rudimentary horn, unicornuate uterus with a non-communicating cavitary rudimentary horn, unicornuate uterus with a communicating cavitary horn, arcuate uterus, uterine didelfus, and T-shaped uterus.

[813] Ovarian diseases and/or disorders include anovulation, polycystic ovary syndrome (Stein-Leventhal syndrome), ovarian cysts, ovarian hypofunction, ovarian insensitivity to gonadotropins, ovarian overproduction of androgens, right ovarian vein syndrome, amenorrhea, hirutism, and ovarian cancer (including, but not limited to, primary and

secondary cancerous growth, Sertoli-Leydig tumors, endometriod carcinoma of the ovary, ovarian papillary serous adenocarcinoma, ovarian mucinous adenocarcinoma, and Ovarian Krukenberg tumors).

[814] Cervical diseases and/or disorders include cervicitis, chronic cervicitis, mucopurulent cervicitis, cervical dysplasia, cervical polyps, Nabothian cysts, cervical erosion, cervical incompetence, and cervical neoplasms (including, for example, cervical carcinoma, squamous metaplasia, squamous cell carcinoma, adenosquamous cell neoplasia, and columnar cell neoplasia).

[815] Additionally, diseases and/or disorders of the reproductive system include disorders and/or diseases of pregnancy, including miscarriage and stillbirth, such as early abortion, late abortion, spontaneous abortion, induced abortion, therapeutic abortion, threatened abortion, missed abortion, incomplete abortion, complete abortion, habitual abortion, missed abortion, and septic abortion; ectopic pregnancy, anemia, Rh incompatibility, vaginal bleeding during pregnancy, gestational diabetes, intrauterine growth retardation, polyhydramnios, HELLP syndrome, abruptio placentae, placenta previa, hyperemesis, preeclampsia, eclampsia, herpes gestationis, and urticaria of pregnancy. Additionally, the polynucleotides, polypeptides, and agonists or antagonists of the present invention may be used in the diagnosis, treatment, and/or prevention of diseases that can complicate pregnancy, including heart disease, heart failure, rheumatic heart disease, congenital heart disease, mitral valve prolapse, high blood pressure, anemia, kidney disease, infectious disease (e.g., rubella, cytomegalovirus, toxoplasmosis, infectious hepatitis, chlamydia, HIV, AIDS, and genital herpes), diabetes mellitus, Graves' disease, thyroiditis, hypothyroidism, Hashimoto's thyroiditis, chronic active hepatitis, cirrhosis of the liver, primary biliary cirrhosis, asthma, systemic lupus eryematosis, rheumatoid arthritis, myasthenia gravis, idiopathic thrombocytopenic purpura, appendicitis, ovarian cysts, gallbladder disorders,and obstruction of the intestine.

[816] Complications associated with labor and parturition include premature rupture of the membranes, pre-term labor, post-term pregnancy, postmaturity, labor that progresses too slowly, fetal distress (e.g., abnormal heart rate (fetal or maternal), breathing problems, and abnormal fetal position), shoulder dystocia, prolapsed umbilical cord, amniotic fluid embolism, and aberrant uterine bleeding.

[817] Further, diseases and/or disorders of the postdelivery period, including endometritis, myometritis, parametritis, peritonitis, pelvic thrombophlebitis, pulmonary embolism, endotoxemia, pyelonephritis, saphenous thrombophlebitis, mastitis, cystitis, postpartum hemorrhage, and inverted uterus.

[818] Other disorders and/or diseases of the female reproductive system that may be diagnosed, treated, and/or prevented by the polynucleotides, polypeptides, and agonists or antagonists of the present invention include, for example, Turner's syndrome, pseudohermaphroditism, premenstrual syndrome, pelvic inflammatory disease, pelvic congestion (vascular engorgement), frigidity, anorgasmia, dyspareunia, ruptured fallopian tube, and Mittelschmerz.

Infectious Disease

[819] Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention can be used to treat or detect infectious agents. For example, by increasing the immune response, particularly increasing the proliferation and differentiation of B and/or T cells, infectious diseases may be treated. The immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may also directly inhibit the infectious agent, without necessarily eliciting an immune response.

[820] Viruses are one example of an infectious agent that can cause disease or symptoms that can be treated or detected by a polynucleotide or polypeptide and/or agonist or antagonist of the present invention. Examples of viruses, include, but are not limited to Examples of viruses, include, but are not limited to the following DNA and RNA viruses and viral families: Arbovirus, Adenoviridae, Arenaviridae, Arterivirus, Birnaviridae, Bunyaviridae, Caliciviridae, Circoviridae, Coronaviridae, Dengue, EBV, HIV, Flaviviridae, Hepadnaviridae (Hepatitis), Herpesviridae (such as, Cytomegalovirus, Herpes Simplex, Herpes Zoster), Mononegavirus (e.g., Paramyxoviridae, Morbillivirus, Rhabdoviridae), Orthomyxoviridae (e.g., Influenza A, Influenza B, and parainfluenza), Papiloma virus, Papovaviridae, Parvoviridae, Picornaviridae, Poxviridae (such as Smallpox or Vaccinia), Reoviridae (e.g., Rotavirus), Retroviridae (HTLV-I, HTLV-II, Lentivirus), and Togaviridae (e.g., Rubivirus).

Viruses falling within these families can cause a variety of diseases or symptoms, including, but not limited to: arthritis, bronchiollitis, respiratory syncytial virus, encephalitis, eye infections (e.g., conjunctivitis, keratitis), chronic fatigue syndrome, hepatitis (A, B, C, E, Chronic Active, Delta), Japanese B encephalitis, Junin, Chikungunya, Rift Valley fever, yellow fever, meningitis, opportunistic infections (e.g., AIDS), pneumonia, Burkitt's Lymphoma, chickenpox, hemorrhagic fever, Measles, Mumps, Parainfluenza, Rabies, the common cold, Polio, leukemia, Rubella, sexually transmitted diseases, skin diseases (e.g., Kaposi's, warts), and viremia. polynucleotides or polypeptides, or agonists or antagonists of the invention, can be used to treat or detect any of these symptoms or diseases. In specific embodiments, polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat: meningitis, Dengue, EBV, and/or hepatitis (e.g., hepatitis B). In an additional specific embodiment polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat patients nonresponsive to one or more other commercially available hepatitis vaccines. In a further specific embodiment polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat AIDS.

[821] Similarly, bacterial and fungal agents that can cause disease or symptoms and that can be treated or detected by a polynucleotide or polypeptide and/or agonist or antagonist of the present invention include, but not limited to, the following Gram-Negative and Gram-positive bacteria, bacterial families, and fungi: Actinomyces (e.g., Norcardia), Acinetobacter, *Cryptococcus neoformans*, Aspergillus, Bacillaceae (e.g., *Bacillus anthrasis*), Bacteroides (e.g., *Bacteroides fragilis*), Blastomycosis, Bordetella, Borrelia (e.g., *Borrelia burgdorferi*), Brucella, Candidia, Campylobacter, Chlamydia, Clostridium (e.g., *Clostridium botulinum*, *Clostridium dificile*, *Clostridium perfringens*, *Clostridium tetani*), Coccidioides, Corynebacterium (e.g., *Corynebacterium diptheriae*), Cryptococcus, Dermatocycoses, *E. coli* (e.g., Enterotoxigenic *E. coli* and Enterohemorrhagic *E. coli*), Enterobacter (e.g. *Enterobacter aerogenes*), Enterobacteriaceae (Klebsiella, Salmonella (e.g., *Salmonella typhi*, *Salmonella enteritidis*, *Salmonella typhi*), Serratia, Yersinia, Shigella), Erysipelothrix, Haemophilus (e.g., *Haemophilus influenza* type B), Helicobacter, Legionella (e.g., *Legionella pneumophila*), Leptospira, Listeria (e.g., *Listeria monocytogenes*), Mycoplasma, Mycobacterium (e.g., *Mycobacterium leprae and Mycobacterium tuberculosis)*, Vibrio (e.g., *Vibrio cholerae)*, Neisseriaceae (e.g., *Neisseria gonorrhea*, *Neisseria meningitidis*), Pasteurellacea, Proteus, Pseudomonas (e.g., *Pseudomonas aeruginosa*), Rickettsiaceae,

Spirochetes (e.g., Treponema spp., Leptospira spp., Borrelia spp.), Shigella spp., Staphylococcus (e.g., *Staphylococcus aureus*), Meningiococcus, Pneumococcus and Streptococcus (e.g., *Streptococcus pneumoniae* and Groups A, B, and C Streptococci), and Ureaplasmas. These bacterial, parasitic, and fungal families can cause diseases or symptoms, including, but not limited to: antibiotic-resistant infections, bacteremia, endocarditis, septicemia, eye infections (e.g., conjunctivitis), uveitis, tuberculosis, gingivitis, bacterial diarrhea, opportunistic infections (e.g., AIDS related infections), paronychia, prosthesis-related infections, dental caries, Reiter's Disease, respiratory tract infections, such as Whooping Cough or Empyema, sepsis, Lyme Disease, Cat-Scratch Disease, dysentery, paratyphoid fever, food poisoning, Legionella disease, chronic and acute inflammation, erythema, yeast infections, typhoid, pneumonia, gonorrhea, meningitis (e.g., mengitis types A and B), chlamydia, syphillis, diphtheria, leprosy, brucellosis, peptic ulcers, anthrax, spontaneous abortions, birth defects, pneumonia, lung infections, ear infections, deafness, blindness, lethargy, malaise, vomiting, chronic diarrhea, Crohn's disease, colitis, vaginosis, sterility, pelvic inflammatory diseases, candidiasis, paratuberculosis, tuberculosis, lupus, botulism, gangrene, tetanus, impetigo, Rheumatic Fever, Scarlet Fever, sexually transmitted diseases, skin diseases (e.g., cellulitis, dermatocycoses), toxemia, urinary tract infections, wound infections, noscomial infections. Polynucleotides or polypeptides, agonists or antagonists of the invention, can be used to treat or detect any of these symptoms or diseases. In specific embodiments, polynucleotides, polypeptides, agonists or antagonists of the invention are used to treat: tetanus, diptheria, botulism, and/or meningitis type B.

[822] Moreover, parasitic agents causing disease or symptoms that can be treated, prevented, and/or diagnosed by a polynucleotide or polypeptide and/or agonist or antagonist of the present invention include, but not limited to, the following families or class: Amebiasis, Babesiosis, Coccidiosis, Cryptosporidiosis, Dientamoebiasis, Dourine, Ectoparasitic, Giardias, Helminthiasis, Leishmaniasis, Schistisoma, Theileriasis, Toxoplasmosis, Trypanosomiasis, and Trichomonas and Sporozoans (e.g., *Plasmodium virax*, *Plasmodium falciparium*, *Plasmodium malariae* and *Plasmodium ovale*). These parasites can cause a variety of diseases or symptoms, including, but not limited to: Scabies, Trombiculiasis, eye infections, intestinal disease (e.g., dysentery, giardiasis), liver disease, lung disease, opportunistic infections (e.g., AIDS related), malaria, pregnancy complications, and toxoplasmosis. polynucleotides or polypeptides, or agonists or antagonists of the

invention, can be used to treat, prevent, and/or diagnose any of these symptoms or diseases. In specific embodiments, polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat, prevent, and/or diagnose malaria.

[823] Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention of the present invention could either be by administering an effective amount of a polypeptide to the patient, or by removing cells from the patient, supplying the cells with a polynucleotide of the present invention, and returning the engineered cells to the patient (ex vivo therapy). Moreover, the polypeptide or polynucleotide of the present invention can be used as an antigen in a vaccine to raise an immune response against infectious disease.

Regeneration

[824] Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention can be used to differentiate, proliferate, and attract cells, leading to the regeneration of tissues. (See, Science 276:59-87 (1997)). The regeneration of tissues could be used to repair, replace, or protect tissue damaged by congenital defects, trauma (wounds, burns, incisions, or ulcers), age, disease (e.g. osteoporosis, osteocarthritis, periodontal disease, liver failure), surgery, including cosmetic plastic surgery, fibrosis, reperfusion injury, or systemic cytokine damage.

[825] Tissues that could be regenerated using the present invention include organs (e.g., pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac), vasculature (including vascular and lymphatics), nervous, hematopoietic, and skeletal (bone, cartilage, tendon, and ligament) tissue. Preferably, regeneration occurs without or decreased scarring. Regeneration also may include angiogenesis.

[826] Moreover, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may increase regeneration of tissues difficult to heal. For example, increased tendon/ligament regeneration would quicken recovery time after damage. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention could also be used prophylactically in an effort to avoid damage. Specific diseases that could be treated include of tendinitis, carpal tunnel syndrome, and other tendon or ligament defects. A further example of tissue regeneration of non-healing wounds includes pressure ulcers, ulcers associated with vascular insufficiency, surgical, and traumatic wounds.

[827] Similarly, nerve and brain tissue could also be regenerated by using polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, to proliferate and differentiate nerve cells. Diseases that could be treated using this method include central and peripheral nervous system diseases, neuropathies, or mechanical and traumatic disorders (e.g., spinal cord disorders, head trauma, cerebrovascular disease, and stoke). Specifically, diseases associated with peripheral nerve injuries, peripheral neuropathy (e.g., resulting from chemotherapy or other medical therapies), localized neuropathies, and central nervous system diseases (e.g., Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome), could all be treated using the polynucleotides or polypeptides, as well as agonists or antagonists of the present invention.

Gastrointestinal Disorders

[828] Polynucleotides or polypeptides, or agonists or antagonists of the present invention, may be used to treat, prevent, diagnose, and/or prognose gastrointestinal disorders, including inflammatory diseases and/or conditions, infections, cancers (e.g., intestinal neoplasms (carcinoid tumor of the small intestine, non-Hodgkin's lymphoma of the small intestine, small bowl lymphoma)), and ulcers, such as peptic ulcers.

[829] Gastrointestinal disorders include dysphagia, odynophagia, inflammation of the esophagus, peptic esophagitis, gastric reflux, submucosal fibrosis and stricturing, Mallory-Weiss lesions, leiomyomas, lipomas, epidermal cancers, adeoncarcinomas, gastric retention disorders, gastroenteritis, gastric atrophy, gastric/stomach cancers, polyps of the stomach, autoimmune disorders such as pernicious anemia, pyloric stenosis, gastritis (bacterial, viral, eosinophilic, stress-induced, chronic erosive, atrophic, plasma cell, and Ménétrier's), and peritoneal diseases (e.g., chyloperioneum, hemoperitoneum, mesenteric cyst, mesenteric lymphadenitis, mesenteric vascular occlusion, panniculitis, neoplasms, peritonitis, pneumoperitoneum, bubphrenic abscess,).

[830] Gastrointestinal disorders also include disorders associated with the small intestine, such as malabsorption syndromes, distension, irritable bowel syndrome, sugar intolerance, celiac disease, duodenal ulcers, duodenitis, tropical sprue, Whipple's disease, intestinal lymphangiectasia, Crohn's disease, appendicitis, obstructions of the ileum, Meckel's

diverticulum, multiple diverticula, failure of complete rotation of the small and large intestine, lymphoma, and bacterial and parasitic diseases (such as Traveler's diarrhea, typhoid and paratyphoid, cholera, infection by Roundworms (*Ascariasis lumbricoides*), Hookworms (*Ancylostoma duodenale*), Threadworms (*Enterobius vermicularis*), Tapeworms (*Taenia saginata, Echinococcus granulosus, Diphyllobothrium spp*., and *T. solium*).

[831] Liver diseases and/or disorders include intrahepatic cholestasis (alagille syndrome, biliary liver cirrhosis), fatty liver (alcoholic fatty liver, reye syndrome), hepatic vein thrombosis, hepatolentricular degeneration, hepatomegaly, hepatopulmonary syndrome, hepatorenal syndrome, portal hypertension (esophageal and gastric varices), liver abscess (amebic liver abscess), liver cirrhosis (alcoholic, biliary and experimental), alcoholic liver diseases (fatty liver, hepatitis, cirrhosis), parasitic (hepatic echinococcosis, fascioliasis, amebic liver abscess), jaundice (hemolytic, hepatocellular, and cholestatic), cholestasis, portal hypertension, liver enlargement, ascites, hepatitis (alcoholic hepatitis, animal hepatitis, chronic hepatitis (autoimmune, hepatitis B, hepatitis C, hepatitis D, drug induced), toxic hepatitis, viral human hepatitis (hepatitis A, hepatitis B, hepatitis C, hepatitis D, hepatitis E), Wilson's disease, granulomatous hepatitis, secondary biliary cirrhosis, hepatic encephalopathy, portal hypertension, varices, hepatic encephalopathy, primary biliary cirrhosis, primary sclerosing cholangitis, hepatocellular adenoma, hemangiomas, bile stones, liver failure (hepatic encephalopathy, acute liver failure), and liver neoplasms (angiomyolipoma, calcified liver metastases, cystic liver metastases, epithelial tumors, fibrolamellar hepatocarcinoma, focal nodular hyperplasia, hepatic adenoma, hepatobiliary cystadenoma, hepatoblastoma, hepatocellular carcinoma, hepatoma, liver cancer, liver hemangioendothelioma, mesenchymal hamartoma, mesenchymal tumors of liver, nodular regenerative hyperplasia, benign liver tumors (Hepatic cysts [Simple cysts, Polycystic liver disease, Hepatobiliary cystadenoma, Choledochal cyst], Mesenchymal tumors [Mesenchymal hamartoma, Infantile hemangioendothelioma, Hemangioma, Peliosis hepatis, Lipomas, Inflammatory pseudotumor, Miscellaneous], Epithelial tumors [Bile duct epithelium (Bile duct hamartoma, Bile duct adenoma), Hepatocyte (Adenoma, Focal nodular hyperplasia, Nodular regenerative hyperplasia)], malignant liver tumors [hepatocellular, hepatoblastoma, hepatocellular carcinoma, cholangiocellular, cholangiocarcinoma, cystadenocarcinoma, tumors of blood vessels, angiosarcoma, Karposi's sarcoma, hemangioendothelioma, other tumors, embryonal sarcoma, fibrosarcoma, leiomyosarcoma, rhabdomyosarcoma,

carcinosarcoma, teratoma, carcinoid, squamous carcinoma, primary lymphoma]), peliosis hepatis, erythrohepatic porphyria, hepatic porphyria (acute intermittent porphyria, porphyria cutanea tarda), Zellweger syndrome).

[832] Pancreatic diseases and/or disorders include acute pancreatitis, chronic pancreatitis (acute necrotizing pancreatitis, alcoholic pancreatitis), neoplasms (adenocarcinoma of the pancreas, cystadenocarcinoma, insulinoma, gastrinoma, and glucagonoma, cystic neoplasms, islet-cell tumors, pancreoblastoma), and other pancreatic diseases (e.g., cystic fibrosis, cyst (pancreatic pseudocyst, pancreatic fistula, insufficiency)).

[833] Gallbladder diseases include gallstones (cholelithiasis and choledocholithiasis), postcholecystectomy syndrome, diverticulosis of the gallbladder, acute cholecystitis, chronic cholecystitis, bile duct tumors, and mucocele.

[834] Diseases and/or disorders of the large intestine include antibiotic-associated colitis, diverticulitis, ulcerative colitis, acquired megacolon, abscesses, fungal and bacterial infections, anorectal disorders (e.g., fissures, hemorrhoids), colonic diseases (colitis, colonic neoplasms [colon cancer, adenomatous colon polyps (e.g., villous adenoma), colon carcinoma, colorectal cancer], colonic diverticulitis, colonic diverticulosis, megacolon [Hirschsprung disease, toxic megacolon]; sigmoid diseases [proctocolitis, sigmoin neoplasms]), constipation, Crohn's disease, diarrhea (infantile diarrhea, dysentery), duodenal diseases (duodenal neoplasms, duodenal obstruction, duodenal ulcer, duodenitis), enteritis (enterocolitis), HIV enteropathy, ileal diseases (ileal neoplasms, ileitis), immunoproliferative small intestinal disease, inflammatory bowel disease (ulcerative colitis, Crohn's disease), intestinal atresia, parasitic diseases (anisakiasis, balantidiasis, blastocystis infections, cryptosporidiosis, dientamoebiasis, amebic dysentery, giardiasis), intestinal fistula (rectal fistula), intestinal neoplasms (cecal neoplasms, colonic neoplasms, duodenal neoplasms, ileal neoplasms, intestinal polyps, jejunal neoplasms, rectal neoplasms), intestinal obstruction (afferent loop syndrome, duodenal obstruction, impacted feces, intestinal pseudo-obstruction [cecal volvulus], intussusception), intestinal perforation, intestinal polyps (colonic polyps, gardner syndrome, peutz-jeghers syndrome), jejunal diseases (jejunal neoplasms), malabsorption syndromes (blind loop syndrome, celiac disease, lactose intolerance, short bowl syndrome, tropical sprue, whipple's disease), mesenteric vascular occlusion, pneumatosis cystoides intestinalis, protein-losing enteropathies (intestinal lymphagiectasis), rectal diseases (anus diseases, fecal incontinence, hemorrhoids, proctitis, rectal fistula, rectal

prolapse, rectocele), peptic ulcer (duodenal ulcer, peptic esophagitis, hemorrhage, perforation, stomach ulcer, Zollinger-Ellison syndrome), postgastrectomy syndromes (dumping syndrome), stomach diseases (e.g., achlorhydria, duodenogastric reflux (bile reflux), gastric antral vascular ectasia, gastric fistula, gastric outlet obstruction, gastritis (atrophic or hypertrophic), gastroparesis, stomach dilatation, stomach diverticulum, stomach neoplasms (gastric cancer, gastric polyps, gastric adenocarcinoma, hyperplastic gastric polyp), stomach rupture, stomach ulcer, stomach volvulus), tuberculosis, visceroptosis, vomiting (e.g., hematemesis, hyperemesis gravidarum, postoperative nausea and vomiting) and hemorrhagic colitis.

[835] Further diseases and/or disorders of the gastrointestinal system include biliary tract diseases, such as, gastroschisis, fistula (e.g., biliary fistula, esophageal fistula, gastric fistula, intestinal fistula, pancreatic fistula), neoplasms (e.g., biliary tract neoplasms, esophageal neoplasms, such as adenocarcinoma of the esophagus, esophageal squamous cell carcinoma, gastrointestinal neoplasms, pancreatic neoplasms, such as adenocarcinoma of the pancreas, mucinous cystic neoplasm of the pancreas, pancreatic cystic neoplasms, pancreatoblastoma, and peritoneal neoplasms), esophageal disease (e.g., bullous diseases, candidiasis, glycogenic acanthosis, ulceration, barrett esophagus varices, atresia, cyst, diverticulum (e.g., Zenker's diverticulum), fistula (e.g., tracheoesophageal fistula), motility disorders (e.g., CREST syndrome, deglutition disorders, achalasia, spasm, gastroesophageal reflux), neoplasms, perforation (e.g., Boerhaave syndrome, Mallory-Weiss syndrome), stenosis, esophagitis, diaphragmatic hernia (e.g., hiatal hernia); gastrointestinal diseases, such as, gastroenteritis (e.g., cholera morbus, norwalk virus infection), hemorrhage (e.g., hematemesis, melena, peptic ulcer hemorrhage), stomach neoplasms (gastric cancer, gastric polyps, gastric adenocarcinoma, stomach cancer)), hernia (e.g., congenital diaphragmatic hernia, femoral hernia, inguinal hernia, obturator hernia, umbilical hernia, ventral hernia), and intestinal diseases (e.g., cecal diseases (appendicitis, cecal neoplasms)).

<u>Chemotaxis</u>

[836] Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may have chemotaxis activity. A chemotaxic molecule attracts or mobilizes cells (e.g., monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or

endothelial cells) to a particular site in the body, such as inflammation, infection, or site of hyperproliferation. The mobilized cells can then fight off and/or heal the particular trauma or abnormality.

[837] Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may increase chemotaxic activity of particular cells. These chemotactic molecules can then be used to treat inflammation, infection, hyperproliferative disorders, or any immune system disorder by increasing the number of cells targeted to a particular location in the body. For example, chemotaxic molecules can be used to treat wounds and other trauma to tissues by attracting immune cells to the injured location. Chemotactic molecules of the present invention can also attract fibroblasts, which can be used to treat wounds.

[838] It is also contemplated that polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may inhibit chemotactic activity. These molecules could also be used to treat disorders. Thus, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention could be used as an inhibitor of chemotaxis.

Binding Activity

[839] A polypeptide of the present invention may be used to screen for molecules that bind to the polypeptide or for molecules to which the polypeptide binds. The binding of the polypeptide and the molecule may activate (agonist), increase, inhibit (antagonist), or decrease activity of the polypeptide or the molecule bound. Examples of such molecules include antibodies, oligonucleotides, proteins (e.g., receptors),or small molecules.

[840] Preferably, the molecule is closely related to the natural ligand of the polypeptide, e.g., a fragment of the ligand, or a natural substrate, a ligand, a structural or functional mimetic. (See, Coligan et al., Current Protocols in Immunology 1(2):Chapter 5 (1991)). Similarly, the molecule can be closely related to the natural receptor to which the polypeptide binds, or at least, a fragment of the receptor capable of being bound by the polypeptide (e.g., active site). In either case, the molecule can be rationally designed using known techniques.

[841] Preferably, the screening for these molecules involves producing appropriate cells which express the polypeptide. Preferred cells include cells from mammals, yeast, Drosophila, or *E. coli*. Cells expressing the polypeptide (or cell membrane containing the expressed polypeptide) are then preferably contacted with a test compound potentially

containing the molecule to observe binding, stimulation, or inhibition of activity of either the polypeptide or the molecule.

[842] The assay may simply test binding of a candidate compound to the polypeptide, wherein binding is detected by a label, or in an assay involving competition with a labeled competitor. Further, the assay may test whether the candidate compound results in a signal generated by binding to the polypeptide.

[843] Alternatively, the assay can be carried out using cell-free preparations, polypeptide/molecule affixed to a solid support, chemical libraries, or natural product mixtures. The assay may also simply comprise the steps of mixing a candidate compound with a solution containing a polypeptide, measuring polypeptide/molecule activity or binding, and comparing the polypeptide/molecule activity or binding to a standard.

[844] Preferably, an ELISA assay can measure polypeptide level or activity in a sample (e.g., biological sample) using a monoclonal or polyclonal antibody. The antibody can measure polypeptide level or activity by either binding, directly or indirectly, to the polypeptide or by competing with the polypeptide for a substrate.

[845] Additionally, the receptor to which the polypeptide of the present invention binds can be identified by numerous methods known to those of skill in the art, for example, ligand panning and FACS sorting (Coligan, et al., Current Protocols in Immun., 1(2), Chapter 5, (1991)). For example, expression cloning is employed wherein polyadenylated RNA is prepared from a cell responsive to the polypeptides, for example, NIH3T3 cells which are known to contain multiple receptors for the FGF family proteins, and SC-3 cells, and a cDNA library created from this RNA is divided into pools and used to transfect COS cells or other cells that are not responsive to the polypeptides. Transfected cells which are grown on glass slides are exposed to the polypeptide of the present invention, after they have been labeled. The polypeptides can be labeled by a variety of means including iodination or inclusion of a recognition site for a site-specific protein kinase.

[846] Following fixation and incubation, the slides are subjected to auto-radiographic analysis. Positive pools are identified and sub-pools are prepared and re-transfected using an iterative sub-pooling and re-screening process, eventually yielding a single clone that encodes the putative receptor.

[847] As an alternative approach for receptor identification, the labeled polypeptides can be photoaffinity linked with cell membrane or extract preparations that express the receptor

molecule. Cross-linked material is resolved by PAGE analysis and exposed to X-ray film. The labeled complex containing the receptors of the polypeptides can be excised, resolved into peptide fragments, and subjected to protein microsequencing. The amino acid sequence obtained from microsequencing would be used to design a set of degenerate oligonucleotide probes to screen a cDNA library to identify the genes encoding the putative receptors.

[848] Moreover, the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling") may be employed to modulate the activities of the polypeptide of the present invention thereby effectively generating agonists and antagonists of the polypeptide of the present invention. *See generally*, U.S. Patent Nos. 5,605,793, 5,811,238, 5,830,721, 5,834,252, and 5,837,458, and Patten, P. A., *et al., Curr. Opinion Biotechnol.* 8:724-33 (1997); Harayama, S. *Trends Biotechnol.* 16(2):76-82 (1998); Hansson, L. O., *et al., J. Mol. Biol.* 287:265-76 (1999); and Lorenzo, M. M. and Blasco, R. *Biotechniques* 24(2):308-13 (1998); each of these patents and publications are hereby incorporated by reference). In one embodiment, alteration of polynucleotides and corresponding polypeptides may be achieved by DNA shuffling. DNA shuffling involves the assembly of two or more DNA segments into a desired molecule by homologous, or site-specific, recombination. In another embodiment, polynucleotides and corresponding polypeptides may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. In another embodiment, one or more components, motifs, sections, parts, domains, fragments, etc., of the polypeptide of the present invention may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules. In preferred embodiments, the heterologous molecules are family members. In further preferred embodiments, the heterologous molecule is a growth factor such as, for example, platelet-derived growth factor (PDGF), insulin-like growth factor (IGF-I), transforming growth factor (TGF)-alpha, epidermal growth factor (EGF), fibroblast growth factor (FGF), TGF-beta, bone morphogenetic protein (BMP)-2, BMP-4, BMP-5, BMP-6, BMP-7, activins A and B, decapentaplegic(dpp), 60A, OP-2, dorsalin, growth differentiation factors (GDFs), nodal, MIS, inhibin-alpha, TGF-beta1, TGF-beta2, TGF-beta3, TGF-beta5, and glial-derived neurotrophic factor (GDNF).

[849] Other preferred fragments are biologically active fragments of the polypeptide of the present invention. Biologically active fragments are those exhibiting activity similar, but

not necessarily identical, to an activity of the polypeptide of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.

[850] Additionally, this invention provides a method of screening compounds to identify those which modulate the action of the polypeptide of the present invention. An example of such an assay comprises combining a mammalian fibroblast cell, a the polypeptide of the present invention, the compound to be screened and ^{3}[H] thymidine under cell culture conditions where the fibroblast cell would normally proliferate. A control assay may be performed in the absence of the compound to be screened and compared to the amount of fibroblast proliferation in the presence of the compound to determine if the compound stimulates proliferation by determining the uptake of ^{3}[H] thymidine in each case. The amount of fibroblast cell proliferation is measured by liquid scintillation chromatography which measures the incorporation of ^{3}[H] thymidine. Both agonist and antagonist compounds may be identified by this procedure.

[851] In another method, a mammalian cell or membrane preparation expressing a receptor for a polypeptide of the present invention is incubated with a labeled polypeptide of the present invention in the presence of the compound. The ability of the compound to enhance or block this interaction could then be measured. Alternatively, the response of a known second messenger system following interaction of a compound to be screened and the receptor is measured and the ability of the compound to bind to the receptor and elicit a second messenger response is measured to determine if the compound is a potential agonist or antagonist. Such second messenger systems include but are not limited to, cAMP guanylate cyclase, ion channels or phosphoinositide hydrolysis.

[852] All of these above assays can be used as diagnostic or prognostic markers. The molecules discovered using these assays can be used to treat disease or to bring about a particular result in a patient (e.g., blood vessel growth) by activating or inhibiting the polypeptide/molecule. Moreover, the assays can discover agents which may inhibit or enhance the production of the polypeptides of the invention from suitably manipulated cells or tissues.

[853] Therefore, the invention includes a method of identifying compounds which bind to a polypeptide of the invention comprising the steps of: (a) incubating a candidate binding

compound with a polypeptide of the present invention; and (b) determining if binding has occurred. Moreover, the invention includes a method of identifying agonists/antagonists comprising the steps of: (a) incubating a candidate compound with a polypeptide of the present invention, (b) assaying a biological activity, and (b) determining if a biological activity of the polypeptide has been altered.

Targeted Delivery

[854] In another embodiment, the invention provides a method of delivering compositions to targeted cells expressing a receptor for a polypeptide of the invention, or cells expressing a cell bound form of a polypeptide of the invention.

[855] As discussed herein, polypeptides or antibodies of the invention may be associated with heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs via hydrophobic, hydrophilic, ionic and/or covalent interactions. In one embodiment, the invention provides a method for the specific delivery of compositions of the invention to cells by administering polypeptides of the invention (including antibodies) that are associated with heterologous polypeptides or nucleic acids. In one example, the invention provides a method for delivering a therapeutic protein into the targeted cell. In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., antisense or ribozymes) or double stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate episomally and that can be transcribed) into the targeted cell.

[856] In another embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention (e.g., polypeptides of the invention or antibodies of the invention) in association with toxins or cytotoxic prodrugs.

[857] By "toxin" is meant compounds that bind and activate endogenous cytotoxic effector systems, radioisotopes, holotoxins, modified toxins, catalytic subunits of toxins, or any molecules or enzymes not normally present in or on the surface of a cell that under defined conditions cause the cell's death. Toxins that may be used according to the methods of the invention include, but are not limited to, radioisotopes known in the art, compounds such as, for example, antibodies (or complement fixing containing portions thereof) that bind an inherent or induced endogenous cytotoxic effector system, thymidine kinase, endonuclease, RNAse, alpha toxin, ricin, abrin, *Pseudomonas* exotoxin A, diphtheria toxin,

saporin, momordin, gelonin, pokeweed antiviral protein, alpha-sarcin and cholera toxin. By "cytotoxic prodrug" is meant a non-toxic compound that is converted by an enzyme, normally present in the cell, into a cytotoxic compound. Cytotoxic prodrugs that may be used according to the methods of the invention include, but are not limited to, glutamyl derivatives of benzoic acid mustard alkylating agent, phosphate derivatives of etoposide or mitomycin C, cytosine arabinoside, daunorubisin, and phenoxyacetamide derivatives of doxorubicin.

Drug Screening

[858] Further contemplated is the use of the polypeptides of the present invention, or the polynucleotides encoding these polypeptides, to screen for molecules which modify the activities of the polypeptides of the present invention. Such a method would include contacting the polypeptide of the present invention with a selected compound(s) suspected of having antagonist or agonist activity, and assaying the activity of these polypeptides following binding.

[859] This invention is particularly useful for screening therapeutic compounds by using the polypeptides of the present invention, or binding fragments thereof, in any of a variety of drug screening techniques. The polypeptide or fragment employed in such a test may be affixed to a solid support, expressed on a cell surface, free in solution, or located intracellularly. One method of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant nucleic acids expressing the polypeptide or fragment. Drugs are screened against such transformed cells in competitive binding assays. One may measure, for example, the formulation of complexes between the agent being tested and a polypeptide of the present invention.

[860] Thus, the present invention provides methods of screening for drugs or any other agents which affect activities mediated by the polypeptides of the present invention. These methods comprise contacting such an agent with a polypeptide of the present invention or a fragment thereof and assaying for the presence of a complex between the agent and the polypeptide or a fragment thereof, by methods well known in the art. In such a competitive binding assay, the agents to screen are typically labeled. Following incubation, free agent is separated from that present in bound form, and the amount of free or uncomplexed label is a

measure of the ability of a particular agent to bind to the polypeptides of the present invention.

[861] Another technique for drug screening provides high throughput screening for compounds having suitable binding affinity to the polypeptides of the present invention, and is described in great detail in European Patent Application 84/03564, published on September 13, 1984, which is incorporated herein by reference herein. Briefly stated, large numbers of different small peptide test compounds are synthesized on a solid substrate, such as plastic pins or some other surface. The peptide test compounds are reacted with polypeptides of the present invention and washed. Bound polypeptides are then detected by methods well known in the art. Purified polypeptides are coated directly onto plates for use in the aforementioned drug screening techniques. In addition, non-neutralizing antibodies may be used to capture the peptide and immobilize it on the solid support.

[862] This invention also contemplates the use of competitive drug screening assays in which neutralizing antibodies capable of binding polypeptides of the present invention specifically compete with a test compound for binding to the polypeptides or fragments thereof. In this manner, the antibodies are used to detect the presence of any peptide which shares one or more antigenic epitopes with a polypeptide of the invention.

Antisense And Ribozyme (Antagonists)

[863] In specific embodiments, antagonists according to the present invention are nucleic acids corresponding to the sequences contained in SEQ ID NO:X, or the complementary strand thereof, and/or to cDNA sequences contained in cDNA plasmid:Z identified for example, in Table 1. In one embodiment, antisense sequence is generated internally, by the organism, in another embodiment, the antisense sequence is separately administered (see, for example, O'Connor, J., Neurochem. 56:560 (1991). Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Antisense technology can be used to control gene expression through antisense DNA or RNA, or through triple-helix formation. Antisense techniques are discussed for example, in Okano, J., Neurochem. 56:560 (1991); Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Triple helix formation is discussed in, for instance, Lee et al., Nucleic Acids Research 6:3073 (1979); Cooney et al., Science 241:456 (1988); and Dervan et

al., Science 251:1300 (1991). The methods are based on binding of a polynucleotide to a complementary DNA or RNA.

[864] For example, the use of c-myc and c-myb antisense RNA constructs to inhibit the growth of the non-lymphocytic leukemia cell line HL-60 and other cell lines was previously described. (Wickstrom et al. (1988); Anfossi et al. (1989)). These experiments were performed in vitro by incubating cells with the oligoribonucleotide. A similar procedure for *in vivo* use is described in WO 91/15580. Briefly, a pair of oligonucleotides for a given antisense RNA is produced as follows: A sequence complimentary to the first 15 bases of the open reading frame is flanked by an EcoR1 site on the 5 end and a HindIII site on the 3 end. Next, the pair of oligonucleotides is heated at 90°C for one minute and then annealed in 2X ligation buffer (20mM TRIS HCl pH 7.5, 10mM MgCl2, 10MM dithiothreitol (DTT) and 0.2 mM ATP) and then ligated to the EcoR1/Hind III site of the retroviral vector PMV7 (WO 91/15580).

[865] For example, the 5' coding portion of a polynucleotide that encodes the polypeptide of the present invention may be used to design an antisense RNA oligonucleotide of from about 10 to 40 base pairs in length. A DNA oligonucleotide is designed to be complementary to a region of the gene involved in transcription thereby preventing transcription and the production of the receptor. The antisense RNA oligonucleotide hybridizes to the mRNA *in vivo* and blocks translation of the mRNA molecule into receptor polypeptide.

[866] In one embodiment, the antisense nucleic acid of the invention is produced intracellularly by transcription from an exogenous sequence. For example, a vector or a portion thereof, is transcribed, producing an antisense nucleic acid (RNA) of the invention. Such a vector would contain a sequence encoding the antisense nucleic acid. Such a vector can remain episomal or become chromosomally integrated, as long as it can be transcribed to produce the desired antisense RNA. Such vectors can be constructed by recombinant DNA technology methods standard in the art. Vectors can be plasmid, viral, or others known in the art, used for replication and expression in vertebrate cells. Expression of the sequence encoding the polypeptide of the present invention or fragments thereof, can be by any promoter known in the art to act in vertebrate, preferably human cells. Such promoters can be inducible or constitutive. Such promoters include, but are not limited to, the SV40 early promoter region (Bernoist and Chambon, Nature 29:304-310 (1981), the promoter contained

in the 3' long terminal repeat of Rous sarcoma virus (Yamamoto et al., Cell 22:787-797 (1980), the herpes thymidine promoter (Wagner et al., Proc. Natl. Acad. Sci. U.S.A. 78:1441-1445 (1981), the regulatory sequences of the metallothionein gene (Brinster, et al., Nature 296:39-42 (1982)), etc.

[867] The antisense nucleic acids of the invention comprise a sequence complementary to at least a portion of an RNA transcript of a gene of the present invention. However, absolute complementarity, although preferred, is not required. A sequence "complementary to at least a portion of an RNA," referred to herein, means a sequence having sufficient complementarity to be able to hybridize with the RNA, forming a stable duplex; in the case of double stranded antisense nucleic acids, a single strand of the duplex DNA may thus be tested, or triplex formation may be assayed. The ability to hybridize will depend on both the degree of complementarity and the length of the antisense nucleic acid. Generally, the larger the hybridizing nucleic acid, the more base mismatches with a RNA it may contain and still form a stable duplex (or triplex as the case may be). One skilled in the art can ascertain a tolerable degree of mismatch by use of standard procedures to determine the melting point of the hybridized complex.

[868] Oligonucleotides that are complementary to the 5' end of the message, e.g., the 5' untranslated sequence up to and including the AUG initiation codon, should work most efficiently at inhibiting translation. However, sequences complementary to the 3' untranslated sequences of mRNAs have been shown to be effective at inhibiting translation of mRNAs as well. See generally, Wagner, R., 1994, Nature 372:333-335. Thus, oligonucleotides complementary to either the 5'- or 3'- non- translated, non-coding regions of polynucleotide sequences described herein could be used in an antisense approach to inhibit translation of endogenous mRNA. Oligonucleotides complementary to the 5' untranslated region of the mRNA should include the complement of the AUG start codon. Antisense oligonucleotides complementary to mRNA coding regions are less efficient inhibitors of translation but could be used in accordance with the invention. Whether designed to hybridize to the 5'-, 3'- or coding region of mRNA of the present invention, antisense nucleic acids should be at least six nucleotides in length, and are preferably oligonucleotides ranging from 6 to about 50 nucleotides in length. In specific aspects the oligonucleotide is at least 10 nucleotides, at least 17 nucleotides, at least 25 nucleotides or at least 50 nucleotides.

[869] The polynucleotides of the invention can be DNA or RNA or chimeric mixtures or

derivatives or modified versions thereof, single-stranded or double-stranded. The oligonucleotide can be modified at the base moiety, sugar moiety, or phosphate backbone, for example, to improve stability of the molecule, hybridization, etc. The oligonucleotide may include other appended groups such as peptides (e.g., for targeting host cell receptors *in vivo*), or agents facilitating transport across the cell membrane (see, e.g., Letsinger et al., 1989, Proc. Natl. Acad. Sci. U.S.A. 86:6553-6556; Lemaitre et al., 1987, Proc. Natl. Acad. Sci. 84:648-652; PCT Publication No. WO88/09810, published December 15, 1988) or the blood-brain barrier (see, e.g., PCT Publication No. WO89/10134, published April 25, 1988), hybridization-triggered cleavage agents. (See, e.g., Krol et al., 1988, BioTechniques 6:958-976) or intercalating agents. (See, e.g., Zon, 1988, Pharm. Res. 5:539-549). To this end, the oligonucleotide may be conjugated to another molecule, e.g., a peptide, hybridization triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent, etc.

[870] The antisense oligonucleotide may comprise at least one modified base moiety which is selected from the group including, but not limited to, 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xantine, 4-acetylcytosine, 5-(carboxyhydroxylmethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine.

[871] The antisense oligonucleotide may also comprise at least one modified sugar moiety selected from the group including, but not limited to, arabinose, 2-fluoroarabinose, xylulose, and hexose.

[872] In yet another embodiment, the antisense oligonucleotide comprises at least one modified phosphate backbone selected from the group including, but not limited to, a phosphorothioate, a phosphorodithioate, a phosphoramidothioate, a phosphoramidate, a

phosphordiamidate, a methylphosphonate, an alkyl phosphotriester, and a formacetal or analog thereof.

[873] In yet another embodiment, the antisense oligonucleotide is an a-anomeric oligonucleotide. An a-anomeric oligonucleotide forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual b-units, the strands run parallel to each other (Gautier et al., 1987, Nucl. Acids Res. 15:6625-6641). The oligonucleotide is a 2'-0-methylribonucleotide (Inoue et al., 1987, Nucl. Acids Res. 15:6131-6148), or a chimeric RNA-DNA analogue (Inoue et al., 1987, FEBS Lett. 215:327-330).

[874] Polynucleotides of the invention may be synthesized by standard methods known in the art, e.g. by use of an automated DNA synthesizer (such as are commercially available from Biosearch, Applied Biosystems, etc.). As examples, phosphorothioate oligonucleotides may be synthesized by the method of Stein et al. (1988, Nucl. Acids Res. 16:3209), methylphosphonate oligonucleotides can be prepared by use of controlled pore glass polymer supports (Sarin et al., 1988, Proc. Natl. Acad. Sci. U.S.A. 85:7448-7451), etc.

[875] While antisense nucleotides complementary to the coding region sequence could be used, those complementary to the transcribed untranslated region are most preferred.

[876] Potential antagonists according to the invention also include catalytic RNA, or a ribozyme (See, e.g., PCT International Publication WO 90/11364, published October 4, 1990; Sarver et al, Science 247:1222-1225 (1990). While ribozymes that cleave mRNA at site specific recognition sequences can be used to destroy mRNAs, the use of hammerhead ribozymes is preferred. Hammerhead ribozymes cleave mRNAs at locations dictated by flanking regions that form complementary base pairs with the target mRNA. The sole requirement is that the target mRNA have the following sequence of two bases: 5'-UG-3'. The construction and production of hammerhead ribozymes is well known in the art and is described more fully in Haseloff and Gerlach, Nature 334:585-591 (1988). There are numerous potential hammerhead ribozyme cleavage sites within the nucleotide sequence of SEQ ID NO:X. Preferably, the ribozyme is engineered so that the cleavage recognition site is located near the 5' end of the mRNA; i.e., to increase efficiency and minimize the intracellular accumulation of non-functional mRNA transcripts.

[877] As in the antisense approach, the ribozymes of the invention can be composed of modified oligonucleotides (e.g., for improved stability, targeting, etc.) and should be delivered to cells which express *in vivo*. DNA constructs encoding the ribozyme may be

introduced into the cell in the same manner as described above for the introduction of antisense encoding DNA. A preferred method of delivery involves using a DNA construct "encoding" the ribozyme under the control of a strong constitutive promoter, such as, for example, pol III or pol II promoter, so that transfected cells will produce sufficient quantities of the ribozyme to destroy endogenous messages and inhibit translation. Since ribozymes unlike antisense molecules, are catalytic, a lower intracellular concentration is required for efficiency.

[878] Antagonist/agonist compounds may be employed to inhibit the cell growth and proliferation effects of the polypeptides of the present invention on neoplastic cells and tissues, i.e. stimulation of angiogenesis of tumors, and, therefore, retard or prevent abnormal cellular growth and proliferation, for example, in tumor formation or growth.

[879] The antagonist/agonist may also be employed to prevent hyper-vascular diseases, and prevent the proliferation of epithelial lens cells after extracapsular cataract surgery. Prevention of the mitogenic activity of the polypeptides of the present invention may also be desirous in cases such as restenosis after balloon angioplasty.

[880] The antagonist/agonist may also be employed to prevent the growth of scar tissue during wound healing.

[881] The antagonist/agonist may also be employed to treat the diseases described herein.

[882] Thus, the invention provides a method of treating disorders or diseases, including but not limited to the disorders or diseases listed throughout this application, associated with overexpression of a polynucleotide of the present invention by administering to a patient (a) an antisense molecule directed to the polynucleotide of the present invention, and/or (b) a ribozyme directed to the polynucleotide of the present invention.

<u>Binding Peptides and Other Molecules</u>

[883] The invention also encompasses screening methods for identifying polypeptides and nonpolypeptides that bind polypeptides of the invention, and the binding molecules identified thereby. These binding molecules are useful, for example, as agonists and antagonists of the polypeptides of the invention. Such agonists and antagonists can be used, in accordance with the invention, in the therapeutic embodiments described in detail, below.

[884] This method comprises the steps of:

1. contacting polypeptides of the invention with a plurality of molecules; and
2. identifying a molecule that binds the polypeptides of the invention.

[885] The step of contacting the polypeptides of the invention with the plurality of molecules may be effected in a number of ways. For example, one may contemplate immobilizing the polypeptides on a solid support and bringing a solution of the plurality of molecules in contact with the immobilized polypeptides. Such a procedure would be akin to an affinity chromatographic process, with the affinity matrix being comprised of the immobilized polypeptides of the invention. The molecules having a selective affinity for the polypeptides can then be purified by affinity selection. The nature of the solid support, process for attachment of the polypeptides to the solid support, solvent, and conditions of the affinity isolation or selection are largely conventional and well known to those of ordinary skill in the art.

[886] Alternatively, one may also separate a plurality of polypeptides into substantially separate fractions comprising a subset of or individual polypeptides. For instance, one can separate the plurality of polypeptides by gel electrophoresis, column chromatography, or like method known to those of ordinary skill for the separation of polypeptides. The individual polypeptides can also be produced by a transformed host cell in such a way as to be expressed on or about its outer surface (e.g., a recombinant phage). Individual isolates can then be "probed" by the polypeptides of the invention, optionally in the presence of an inducer should one be required for expression, to determine if any selective affinity interaction takes place between the polypeptides and the individual clone. Prior to contacting the polypeptides with each fraction comprising individual polypeptides, the polypeptides could first be transferred to a solid support for additional convenience. Such a solid support may simply be a piece of filter membrane, such as one made of nitrocellulose or nylon. In this manner, positive clones could be identified from a collection of transformed host cells of an expression library, which harbor a DNA construct encoding a polypeptide having a selective affinity for polypeptides of the invention. Furthermore, the amino acid sequence of the polypeptide having a selective affinity for the polypeptides of the invention can be determined directly by conventional means or the coding sequence of the DNA encoding the polypeptide can frequently be determined more conveniently. The primary sequence can then be deduced from the corresponding DNA sequence. If the amino acid sequence is to be determined from the polypeptide itself, one may use microsequencing techniques. The

sequencing technique may include mass spectroscopy.

[887] In certain situations, it may be desirable to wash away any unbound polypeptides from a mixture of the polypeptides of the invention and the plurality of polypeptides prior to attempting to determine or to detect the presence of a selective affinity interaction. Such a wash step may be particularly desirable when the polypeptides of the invention or the plurality of polypeptides are bound to a solid support.

[888] The plurality of molecules provided according to this method may be provided by way of diversity libraries, such as random or combinatorial peptide or nonpeptide libraries which can be screened for molecules that specifically bind polypeptides of the invention. Many libraries are known in the art that can be used, e.g., chemically synthesized libraries, recombinant (e.g., phage display libraries), and in vitro translation-based libraries. Examples of chemically synthesized libraries are described in Fodor et al., 1991, Science 251:767-773; Houghten et al., 1991, Nature 354:84-86; Lam et al., 1991, Nature 354:82-84; Medynski, 1994, Bio/Technology 12:709-710;Gallop et al., 1994, J. Medicinal Chemistry 37(9):1233-1251; Ohlmeyer et al., 1993, Proc. Natl. Acad. Sci. USA 90:10922-10926; Erb et al., 1994, Proc. Natl. Acad. Sci. USA 91:11422-11426; Houghten et al., 1992, Biotechniques 13:412; Jayawickreme et al., 1994, Proc. Natl. Acad. Sci. USA 91:1614-1618; Salmon et al., 1993, Proc. Natl. Acad. Sci. USA 90:11708-11712; PCT Publication No. WO 93/20242; and Brenner and Lerner, 1992, Proc. Natl. Acad. Sci. USA 89:5381-5383.

[889] Examples of phage display libraries are described in Scott and Smith, 1990, Science 249:386-390; Devlin et al., 1990, Science, 249:404-406; Christian, R. B., et al., 1992, J. Mol. Biol. 227:711-718); Lenstra, 1992, J. Immunol. Meth. 152:149-157; Kay et al., 1993, Gene 128:59-65; and PCT Publication No. WO 94/18318 dated Aug. 18, 1994.

[890] In vitro translation-based libraries include but are not limited to those described in PCT Publication No. WO 91/05058 dated Apr. 18, 1991; and Mattheakis et al., 1994, Proc. Natl. Acad. Sci. USA 91:9022-9026.

[891] By way of examples of nonpeptide libraries, a benzodiazepine library (see e.g., Bunin et al., 1994, Proc. Natl. Acad. Sci. USA 91:4708-4712) can be adapted for use. Peptoid libraries (Simon et al., 1992, Proc. Natl. Acad. Sci. USA 89:9367-9371) can also be used. Another example of a library that can be used, in which the amide functionalities in peptides have been permethylated to generate a chemically transformed combinatorial library, is described by Ostresh et al. (1994, Proc. Natl. Acad. Sci. USA 91:11138-11142).

[892] The variety of non-peptide libraries that are useful in the present invention is great. For example, Ecker and Crooke, 1995, Bio/Technology 13:351-360 list benzodiazepines, hydantoins, piperazinediones, biphenyls, sugar analogs, beta-mercaptoketones, arylacetic acids, acylpiperidines, benzopyrans, cubanes, xanthines, aminimides, and oxazolones as among the chemical species that form the basis of various libraries.

[893] Non-peptide libraries can be classified broadly into two types: decorated monomers and oligomers. Decorated monomer libraries employ a relatively simple scaffold structure upon which a variety functional groups is added. Often the scaffold will be a molecule with a known useful pharmacological activity. For example, the scaffold might be the benzodiazepine structure.

[894] Non-peptide oligomer libraries utilize a large number of monomers that are assembled together in ways that create new shapes that depend on the order of the monomers. Among the monomer units that have been used are carbamates, pyrrolinones, and morpholinos. Peptoids, peptide-like oligomers in which the side chain is attached to the alpha amino group rather than the alpha carbon, form the basis of another version of non-peptide oligomer libraries. The first non-peptide oligomer libraries utilized a single type of monomer and thus contained a repeating backbone. Recent libraries have utilized more than one monomer, giving the libraries added flexibility.

[895] Screening the libraries can be accomplished by any of a variety of commonly known methods. See, e.g., the following references, which disclose screening of peptide libraries: Parmley and Smith, 1989, Adv. Exp. Med. Biol. 251:215-218; Scott and Smith, 1990, Science 249:386-390; Fowlkes et al., 1992; BioTechniques 13:422-427; Oldenburg et al., 1992, Proc. Natl. Acad. Sci. USA 89:5393-5397; Yu et al., 1994, Cell 76:933-945; Staudt et al., 1988, Science 241:577-580; Bock et al., 1992, Nature 355:564-566; Tuerk et al., 1992, Proc. Natl. Acad. Sci. USA 89:6988-6992; Ellington et al., 1992, Nature 355:850-852; U.S. Pat. No. 5,096,815, U.S. Pat. No. 5,223,409, and U.S. Pat. No. 5,198,346, all to Ladner et al.; Rebar and Pabo, 1993, Science 263:671-673; and CT Publication No. WO 94/18318.

[896] In a specific embodiment, screening to identify a molecule that binds polypeptides of the invention can be carried out by contacting the library members with polypeptides of the invention immobilized on a solid phase and harvesting those library members that bind to the polypeptides of the invention. Examples of such screening methods, termed "panning" techniques are described by way of example in Parmley and Smith, 1988, Gene 73:305-318;

Fowlkes et al., 1992, BioTechniques 13:422-427; PCT Publication No. WO 94/18318; and in references cited herein.

[897] In another embodiment, the two-hybrid system for selecting interacting proteins in yeast (Fields and Song, 1989, Nature 340:245-246; Chien et al., 1991, Proc. Natl. Acad. Sci. USA 88:9578-9582) can be used to identify molecules that specifically bind to polypeptides of the invention.

[898] Where the binding molecule is a polypeptide, the polypeptide can be conveniently selected from any peptide library, including random peptide libraries, combinatorial peptide libraries, or biased peptide libraries. The term "biased" is used herein to mean that the method of generating the library is manipulated so as to restrict one or more parameters that govern the diversity of the resulting collection of molecules, in this case peptides.

[899] Thus, a truly random peptide library would generate a collection of peptides in which the probability of finding a particular amino acid at a given position of the peptide is the same for all 20 amino acids. A bias can be introduced into the library, however, by specifying, for example, that a lysine occur every fifth amino acid or that positions 4, 8, and 9 of a decapeptide library be fixed to include only arginine. Clearly, many types of biases can be contemplated, and the present invention is not restricted to any particular bias. Furthermore, the present invention contemplates specific types of peptide libraries, such as phage displayed peptide libraries and those that utilize a DNA construct comprising a lambda phage vector with a DNA insert.

[900] As mentioned above, in the case of a binding molecule that is a polypeptide, the polypeptide may have about 6 to less than about 60 amino acid residues, preferably about 6 to about 10 amino acid residues, and most preferably, about 6 to about 22 amino acids. In another embodiment, a binding polypeptide has in the range of 15-100 amino acids, or 20-50 amino acids.

[901] The selected binding polypeptide can be obtained by chemical synthesis or recombinant expression.

Other Activities

[902] A polypeptide, polynucleotide, agonist, or antagonist of the present invention, as a result of the ability to stimulate vascular endothelial cell growth, may be employed in treatment for stimulating re-vascularization of ischemic tissues due to various disease

conditions such as thrombosis, arteriosclerosis, and other cardiovascular conditions. The polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed to stimulate angiogenesis and limb regeneration, as discussed above.

[903] A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed for treating wounds due to injuries, burns, post-operative tissue repair, and ulcers since they are mitogenic to various cells of different origins, such as fibroblast cells and skeletal muscle cells, and therefore, facilitate the repair or replacement of damaged or diseased tissue.

[904] A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed stimulate neuronal growth and to treat and prevent neuronal damage which occurs in certain neuronal disorders or neuro-degenerative conditions such as Alzheimer's disease, Parkinson's disease, and AIDS-related complex. A polypeptide, polynucleotide, agonist, or antagonist of the present invention may have the ability to stimulate chondrocyte growth, therefore, they may be employed to enhance bone and periodontal regeneration and aid in tissue transplants or bone grafts.

[905] A polypeptide, polynucleotide, agonist, or antagonist of the present invention may be also be employed to prevent skin aging due to sunburn by stimulating keratinocyte growth.

[906] A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed for preventing hair loss, since FGF family members activate hair-forming cells and promotes melanocyte growth. Along the same lines, a polypeptide, polynucleotide, agonist, or antagonist of the present invention may be employed to stimulate growth and differentiation of hematopoietic cells and bone marrow cells when used in combination with other cytokines.

[907] A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed to maintain organs before transplantation or for supporting cell culture of primary tissues. A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed for inducing tissue of mesodermal origin to differentiate in early embryos.

[908] A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also increase or decrease the differentiation or proliferation of embryonic stem cells, besides, as discussed above, hematopoietic lineage.

[909] A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be used to modulate mammalian characteristics, such as body height, weight, hair color, eye color, skin, percentage of adipose tissue, pigmentation, size, and shape (e.g., cosmetic surgery). Similarly, a polypeptide, polynucleotide, agonist, or antagonist of the present invention may be used to modulate mammalian metabolism affecting catabolism, anabolism, processing, utilization, and storage of energy.

[910] A polypeptide, polynucleotide, agonist, or antagonist of the present invention may be used to treat weight disorders, including but not limited to, obesity, cachexia, wasting disease, anorexia, and bulimia.

[911] A polypeptide, polynucleotide, agonist, or antagonist of the present invention may be used to change a mammal's mental state or physical state by influencing biorhythms, caricadic rhythms, depression (including depressive disorders), tendency for violence, tolerance for pain, reproductive capabilities (preferably by Activin or Inhibin-like activity), hormonal or endocrine levels, appetite, libido, memory, stress, or other cognitive qualities.

[912] A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be used as a food additive or preservative, such as to increase or decrease storage capabilities, fat content, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional components.

[913] The above-recited applications have uses in a wide variety of hosts. Such hosts include, but are not limited to, human, murine, rabbit, goat, guinea pig, camel, horse, mouse, rat, hamster, pig, micro-pig, chicken, goat, cow, sheep, dog, cat, non-human primate, and human. In specific embodiments, the host is a mouse, rabbit, goat, guinea pig, chicken, rat, hamster, pig, sheep, dog or cat. In preferred embodiments, the host is a mammal. In most preferred embodiments, the host is a human.

Other Preferred Embodiments

[914] Other preferred embodiments of the claimed invention include an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 50 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X or the complementary strand thereto, and/or cDNA plasmid:V.

[915] Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of positions identified for SEQ ID NO:X in Table 1.

[916] Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 150 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X or the complementary strand thereto, and/or cDNA plasmid:V.

[917] Further preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 500 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X or the complementary strand thereto, and/or cDNA plasmid:V.

[918] A further preferred embodiment is a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the nucleotide sequence of SEQ ID NO:X in the range of positions identified for SEQ ID NO:X in Table 1.

[919] A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence of SEQ ID NO:X or the complementary strand thereto, and/or cDNA plasmid:V.

[920] Also preferred is an isolated nucleic acid molecule which hybridizes under stringent hybridization conditions to a nucleic acid molecule comprising a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto and/or cDNA plasmid:V, wherein said nucleic acid molecule which hybridizes does not hybridize under stringent hybridization conditions to a nucleic acid molecule having a nucleotide sequence consisting of only A residues or of only T residues.

[921] Also preferred is a composition of matter comprising a DNA molecule which comprises cDNA plasmid:V.

[922] Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides in the nucleotide sequence of cDNA plasmid:V.

[923] Also preferred is an isolated nucleic acid molecule, wherein said sequence of at least 50 contiguous nucleotides is included in the nucleotide sequence of an open reading frame sequence encoded by cDNA plasmid:V.

[924] Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 150 contiguous nucleotides in the nucleotide sequence encoded by cDNA plasmid:V.

[925] A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 500 contiguous nucleotides in the nucleotide sequence encoded by cDNA plasmid:V.

[926] A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence encoded by cDNA plasmid:V.

[927] A further preferred embodiment is a method for detecting in a biological sample a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto and a nucleotide sequence encoded by cDNA plasmid:V; which method comprises a step of comparing a nucleotide sequence of at least one nucleic acid molecule in said sample with a sequence selected from said group and determining whether the sequence of said nucleic acid molecule in said sample is at least 95% identical to said selected sequence.

[928] Also preferred is the above method wherein said step of comparing sequences comprises determining the extent of nucleic acid hybridization between nucleic acid molecules in said sample and a nucleic acid molecule comprising said sequence selected from said group. Similarly, also preferred is the above method wherein said step of comparing sequences is performed by comparing the nucleotide sequence determined from a nucleic acid molecule in said sample with said sequence selected from said group. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

[929] A further preferred embodiment is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting nucleic acid molecules in said sample, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto and a nucleotide sequence encoded by cDNA plasmid:V.

[930] The method for identifying the species, tissue or cell type of a biological sample can comprise a step of detecting nucleic acid molecules comprising a nucleotide sequence in

a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

[931] Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto or cDNA plasmid:V which encodes a protein, wherein the method comprises a step of detecting in a biological sample obtained from said subject nucleic acid molecules, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto and a nucleotide sequence of cDNA plasmid:V.

[932] The method for diagnosing a pathological condition can comprise a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

[933] Also preferred is a composition of matter comprising isolated nucleic acid molecules wherein the nucleotide sequences of said nucleic acid molecules comprise a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto and a nucleotide sequence encoded by cDNA plasmid:V. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

[934] Also preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto and/or a polypeptide encoded by cDNA plasmid:V.

[935] Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto and/or a polypeptide encoded by cDNA plasmid:V.

[936] Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino

acid sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto and/or a polypeptide encoded by cDNA plasmid:V.

[937] Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the complete amino acid sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto and/or a polypeptide encoded by cDNA plasmid:V.

[938] Further preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the complete amino acid sequence of a polypeptide encoded by cDNA plasmid:V.

[939] Also preferred is a polypeptide wherein said sequence of contiguous amino acids is included in the amino acid sequence of a portion of said polypeptide encoded by cDNA plasmid:V; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto and/or the polypeptide sequence of SEQ ID NO:Y.

[940] Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of a polypeptide encoded by cDNA plasmid:V..

[941] Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of a polypeptide encoded by cDNA plasmid:V.

[942] Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the amino acid sequence of a polypeptide encoded by cDNA plasmid:V.

[943] Further preferred is an isolated antibody which binds specifically to a polypeptide comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: a polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto and a polypeptide encoded by cDNA plasmid:V.

[944] Further preferred is a method for detecting in a biological sample a polypeptide comprising an amino acid sequence which is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: a polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto and a polypeptide encoded by cDNA plasmid:V; which method comprises a

step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence selected from said group and determining whether the sequence of said polypeptide molecule in said sample is at least 90% identical to said sequence of at least 10 contiguous amino acids.

[945] Also preferred is the above method wherein said step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence selected from said group comprises determining the extent of specific binding of polypeptides in said sample to an antibody which binds specifically to a polypeptide comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: a polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto and a polypeptide encoded by cDNA plasmid:V.

[946] Also preferred is the above method wherein said step of comparing sequences is performed by comparing the amino acid sequence determined from a polypeptide molecule in said sample with said sequence selected from said group.

[947] Also preferred is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting polypeptide molecules in said sample, if any, comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto and a polypeptide encoded by cDNA plasmid:V.

[948] Also preferred is the above method for identifying the species, tissue or cell type of a biological sample, which method comprises a step of detecting polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the above group.

[949] Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a nucleic acid sequence identified in Table 1 encoding a polypeptide, which method comprises a step of detecting in a biological sample obtained from said subject polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence

selected from the group consisting of: polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto and a polypeptide encoded by cDNA plasmid:V.

[950] In any of these methods, the step of detecting said polypeptide molecules includes using an antibody.

[951] Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a nucleotide sequence encoding a polypeptide wherein said polypeptide comprises an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto and a polypeptide encoded by cDNA plasmid:V.

[952] Also preferred is an isolated nucleic acid molecule, wherein said nucleotide sequence encoding a polypeptide has been optimized for expression of said polypeptide in a prokaryotic host.

[953] Also preferred is an isolated nucleic acid molecule, wherein said polypeptide comprises an amino acid sequence selected from the group consisting of: polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto and a polypeptide encoded by cDNA plasmid:V.

[954] Further preferred is a method of making a recombinant vector comprising inserting any of the above isolated nucleic acid molecule into a vector. Also preferred is the recombinant vector produced by this method. Also preferred is a method of making a recombinant host cell comprising introducing the vector into a host cell, as well as the recombinant host cell produced by this method.

[955] Also preferred is a method of making an isolated polypeptide comprising culturing this recombinant host cell under conditions such that said polypeptide is expressed and recovering said polypeptide. Also preferred is this method of making an isolated polypeptide, wherein said recombinant host cell is a eukaryotic cell and said polypeptide is a human protein comprising an amino acid sequence selected from the group consisting of: polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto and a polypeptide encoded by cDNA plasmid:V. The isolated polypeptide produced by this method is also preferred.

[956] Also preferred is a method of treatment of an individual in need of an increased level of a protein activity, which method comprises administering to such an individual a Therapeutic comprising an amount of an isolated polypeptide, polynucleotide, immunogenic fragment or analogue thereof, binding agent, antibody, or antigen binding fragment of the claimed invention effective to increase the level of said protein activity in said individual.

[957] Also preferred is a method of treatment of an individual in need of a decreased level of a protein activity, which method comprised administering to such an individual a Therapeutic comprising an amount of an isolated polypeptide, polynucleotide, immunogenic fragment or analogue thereof, binding agent, antibody, or antigen binding fragment of the claimed invention effective to decrease the level of said protein activity in said individual.

[958] In specific embodiments of the invention, for each "Contig ID" listed in the fourth column of Table 2, preferably excluded are one or more polynucleotides comprising, or alternatively consisting of, a nucleotide sequence referenced in the fifth column of Table 2 and described by the general formula of a-b, whereas a and b are uniquely determined for the corresponding SEQ ID NO:X referred to in column 3 of Table 2. Further specific embodiments are directed to polynucleotide sequences excluding one, two, three, four, or more of the specific polynucleotide sequences referred to in the fifth column of Table 2.

[959] Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of c - d, where both c and d correspond to the positions of nucleotide residues shown in SEQ ID NO:X, and where d is greater than or equal to c + 14.

[960] In no way is this listing meant to encompass all of the sequences which may be excluded by the general formula, it is just a representative example. All references available through these accessions are hereby incorporated by reference in their entirety.

TABLE 2

Gene No.	cDNA Plasmid:V	NT SEQ ID NO: X	Contig ID	Public Accession Numbers
1	HE8NC81	2	1096692	H51315, H51911, AA075579, AA075632, AA171844, AA172293, AA554431, AA291512, AA404609, AA404225, AA411046, AA434329, AA706376, AA953518, AI370413, AI638559, AI539668, AI539195, AI682137, AI683712,

				AI684143, AI686571, AI799522, AI858190, AI859795, AI828762, AI870700, AW073686, AW150534, AW470108, and AW615203.
1	HE8NC81	10	862015	
2	HDPPA04	3	904765	AU135908, AI990290, AW961323, AI798762, AA044757, AW105205, AW197379, AU156359, AA039608, AA247117, AW889458, AA303575, AA036918, AA247128, AI214428, AW449368, AA044631, AI762460, AK001872, and AF142780.
2	HDPPA04	11	905419	AI990290, AW961323, AI798762, AA044757, AW105205, AW197379, AU135908, AU156359, AA039608, AW889458, AA303575, AA036918, AA247117, AI214428, AW449368, AA247128, AA044631, AI762460, AW972092, AW972091, AW968355, AW972093, AW968356, AW968729, AW972090, AW971740, AW969229, AI432644, AI431337, AI623302, AI432662, AI431248, AI431328, BF448552, AI432649, AI431254, AI431243, AI432665, AI431347, AI432653, AI431230, AI432654, AI431354, AI432655, AI431310, AI431312, AI431330, AW081103, AI432651, AI432647, AI432677, AI432661, AI432675, AI492519, AI431241, BF589777, BE672742, BE672792, AI432658, BE672719, AI431357, AI432676, BE672759, AI431351, BE672767, AI432673, AI431345, AI431353, AW128900, AI432672, AI432674, AI431346, AI431255, BE672774, BE672748, BE672743, BE672745, AI431340, BE672738, AW128846, AI432664, BE672732, AI432650, AI791349, AI431307, AI431316, AW128897, BE672749, BE672744, BE672773, AI492520, AI431751, AI492509, AI432643, AI432657, AI492510, AI432666, AW129223, AI431247, BE672626, BE672644, AI431308, BE672625, AW128884, AK001872, AX030435, AX030436, Y17793, AF064854, and AR071207.
2	HDPPA04	12	905418	AU135908, AA247128, AA247117, and AK001872.
3	HTTDB46, HSIDS22	4	812763	
3	HTTDB46, HSIDS22	13	909573	AW629106, AI991125, AA884903, AI339669, AW000848, BF333492, AW966330, AW964468, AW949645, AW966389, AW975618, AV738340, AV724520, AW973541, D80045, AV744690, AV723097, AV742732, C14389, C14331, AW965158, AV702035, AW949642, AV744012, AW366296, D51799, AW973445, AV699550, AV718489, AW964488, AV718692, D59502, D80195, C14429, AV720791, AV741220, AW966050, AW960553, AW965185, AW965197, D80164, AW966053, AW959597, AV719468, AV718800, AW966013, AW949658, AW949643, AW975621, AW966054, AW966534, AV719783, AW960465, AV742048, AW962395, AV720464, AW949654, AV699927, AW966022, AW177440, AW966075, C15076, AW966065, AW966041, D80038, AI905856, AW978648, AV700229, AV719324, AV718440, AW975613, AV720028, D59467, AW966029, AW965196, AW965184, D59275, AW965175, AW966030, AV718770, AV719188, D80227, AW966062, AW964477, AW949641, AW959570, AW949646, AW973334, AW966531, AW978634, AW959062, D80269, D58283, AW956434, AW949630, D80022, AA305409, AW965163, D80166, AW959799, AW966059, D59859, D80193, AW960473,

				D59619, D80210, D80391, AW973474, D80240, AV719822, D59787, D81030, D51423, AW978661, AW973488, AV720211, AV718844, D80253, AV720203, AW964756, AW973307, D80043, AV723927, AV718938, AV718633, AW959628, AW965177, AW975605, AW949656, AW973485, AV718707, AV718931, AV720878, AV719557, AV720731, AW973482, AV699447, AW958992, AW958993, AV722801, AW959136, AW962082, AW959469, AW959202, D80212, AV720150, D80196, D80188, D59610, AW949657, D80366, D50979, D80219, AV705134, AV701004, AW949655, AW375405, D59927, D57483, D80378, D51022, AW962245, AW973330, D59889, D50995, AW960454, D80024, AV720812, AW949653, AW949631, AW949618, AW964737, AV718681, AW966032, AW959582, AW956397, AW949629, AW949633, AW949632, AV700889, AA305578, AW964532, AW973447, AW966043, AV720533, AW753053, AW966023, AV718530, AV721386, AV707024, D80241, AV727990, AV699746, D81026, AV727978, AW960564, AV699669, AV742001, AW960504, AW960532, D51060, AW965176, AV742022, AW973465, AV738928, AW752082, AW753067, AW964541, D80248, AV699866, AW975623, AV705869, AW966332, AV720654, T03269, AW960570, AW178893, AW179328, AA514188, AV701125, AV701166, AV701149, D80251, AV719913, AW960474, AI557751, AV699652, C75259, AW973490, AV701443, AW378532, D80522, AV719049, AW966399, C14014, AW966333, AV742667, AW177501, AV701335, AW966331, AV742430, AK025267, AK025111, AB020625, AC016572, AX047063, A62298, AX047064, A62300, AR070327, A84916, AX047062, A82595, Y17188, AR018138, AX033851, AX020191, AX035434, AR016808, AX020190, AJ302649, Y17187, AX027925, AJ132110, A94995, AF058696, AR087649, A30438, AX021518, AR008278, AB028859, X67155, D26022, A25909, AX028130, A67220, D89785, A78862, D34614, X82626, AR074545, AR016514, Y12724, D88547, AB002449, AR060385, A43190, AR077702, AR092424, X68127, AR025207, AR008443, AR038669, AJ294956, I50126, I50132, I50128, I50133, AR091537, Y08991, AF260572, AR066488, U79457, A44171, AR060138, A45456, A26615, AR052274, AX014811, AR008277, AR008281, AB012117, AR074139, Y09669, A43192, I14842, AR016691, AR016690, U46128, AX015396, AR066487, AR074136, AR054175, AR074141, AJ287395, AR066482, S68736, AR066490, A85396, AR088705, AX042372, D50010, A85477, I19525, I18367, A86792, A63261, X93549, A70867, AR008408, D88507, AR062872, AR093385, AF135125, D13509, A64136, A68321, AR060133, I79511, AR050070, AF217994, AF123263, AR032065, and AR008382.
4	HCECR39	5	1113428	AI885174, AI744622, AA814734, AA729021, AI636514, AI401144, W58757, T17420, H29295, AI271692, AI817490, AA476679, R54385, AA877627, AW195601, AA701423, AA004377, Z40193, AA036722, AA046759, AA004376, R87400, W25867, AA766565, R84338, F06493, R90870, AA322984, AI743101, R68843, AI479057, R34643,

				AA341547, AA946714, R93883, R66774, R58428, AA700399, AA026328, N47479, AI536655, F06935, R94042, W78955, AA652599, U90550, AR036568, U90543, AR036564, U90142, AL021917, U97497, U97495, and AL050330.
4	HCECR39	14	812734	AI885174, AI744622, AA814734, AA729021, AI636514, AI401144, W58757, AA476679, AI271692, T17420, AI817490, H29295, R54385, AA877627, AA701423, AA036722, AA004377, Z40193, AW195601, R84338, AA004376, W25867, R87400, AA766565, F06493, R68843, R90870, AA322984, R34643, AA046759, AI479057, AA341547, R93883, R66774, AI743101, R58428, AA946714, AA700399, AA026328, N47479, AI536655, F06935, R94042, W78955, AA652599, U90550, AR036568, U90543, AR036564, U90142, AL021917, U97497, U97495, and AL050330.
5	HCE2X64	6	1111069	AW157772, AI768325, AW072067, AW163204, D52151, D52158, C14535, D52025, AW090592, D52014, AA916782, C14534, AI268693, AI589300, D51740, D51951, R54483, D59739, H19000, AI341953, AA627910, C14295, T15574, R52319, H49512, H49742, AA907297, AA363868, H41615, H40838, D59792, Z45247, Z41478, D52130, H19101, F08485, D51823, F04956, D51574, AA333764, D59715, T31138, H06704, F04609, C14365, T33909, T34829, AW163729, AW163813, AI681322, AW132034, AI282903, AL121328, AI682743, AI633419, AI569616, AI537677, AI491852, AW129202, AI249257, AI811344, AI828731, AI539771, AI273048, AI591316, AI284020, AW088793, AI590999, AI572676, AI857296, AI799199, AI554427, AI636445, AL043326, AI868831, AW087445, AI922901, AW169671, AL045500, AI539153, AI610645, AI866608, AI612913, AL036396, AI680165, AL119791, AI433157, AI349772, AL036146, AI554484, AI873704, AI610756, AI912866, AI498579, AL121270, AI590021, AL047042, AI687465, AI702406, AI273843, AI811863, AI475451, AW078929, AI499463, AI520785, AI801322, AI682720, AI433976, AI802542, AI224992, AI678302, AI568870, AI612759, AI952360, AW118512, AW131954, AI679321, AI612920, AW196141, AI690312, AI571551, AW168795, AW238730, AI884469, AW002342, AI702433, AW082040, AI269862, AI344817, AI475817, AA427700, AI866002, AI863014, AI680280, AW262565, AI689571, AI859402, AI860537, AI619749, AI636719, AW082060, AI538716, AA225339, AL047763, AW071349, AL036361, AI568296, AI250293, AL036802, AI679916, AI678762, AI570384, AI859511, AI824557, AI673256, AW103893, AI561299, AW150578, AI269696, AI475371, AL135661, AI567360, AI590120, AI690751, AI282504, AI654750, AI474107, AI648684, AI500039, AI567993, AI872711, AI598061, AI888501, AW117882, AI620868, AI571909, AI801608, AW268253, AI434281, AW162071, AW129170, AL045997, AI566507, AI580190, AI801766, AI567351, AW301409, AA640779, AI500077, AI281779, AI701074, AI862144, AI097248, AL045266, AI648663, AI349645, AI580240, AI570909, AI686597, AI573032, AI273142, AW102785, AA470491, AW403717, AI349933, AI445165, AL040243, AI540832, AI446606, AI439087, AW274192, AL040169,

				AI679504, AI613017, AI919345, AI453322, AI684279, AI640379, AL079963, AI920968, AI537075, AI687728, AI492528, AI469532, AI654276, AI274013, AI500146, AW195957, AL036759, AI436456, AI815855, AI624668, AI264741, AW103371, AI521012, AW160386, AI860674, AL048871, AI670782, AI432229, AI064830, AI469811, AI628292, AI745713, AI536638, AI801544, AW151485, AW090013, AI269205, AI800453, AL050342, I48979, I89947, AL122050, AB019565, AF090903, AL050146, AF090934, AF113677, AF104032, AF090900, I48978, AL133016, AL050393, I89931, AF090901, Y11587, E03348, S78214, AF113691, AF113013, AJ242859, AF078844, AL080137, AL133640, S68736, AL137527, AF113019, AL110221, AL050149, A08916, AF118070, A08913, L31396, L31397, AF090943, AF118064, AL110196, AL117457, AF125949, AL122093, AF106862, AF113689, A93016, AL137459, AR059958, X84990, AF017152, AL080060, AL050277, AL049938, AF158248, AL133093, AL133606, AL122121, AL133075, AL096744, AL137557, AF113676, AL080124, AL117460, AL050138, AL050108, AL133557, AF090896, AL133565, AL050116, AF113694, AF111851, AL049452, AL137283, AL122123, Y11254, AF113690, AL133080, AF113699, AL049314, AF091084, U42766, X63574, E07361, AF146568, AJ000937, X82434, Y16645, AF079765, AF125948, AL049300, AL049466, A65341, AR011880, AL117394, U91329, I49625, AL110225, AF017437, E07108, AL049382, AF177401, AL137550, AL117585, AF097996, AL133560, AJ238278, A08910, AL049464, U00763, AL050024, E02349, A08912, AL049430, AL122098, AL117435, AL117583, AF067728, AF118094, AF183393, A77033, A77035, AF087943, I33392, X65873, X72889, A58524, A58523, AL049283, A08909, Z82022, A12297, AL137648, I03321, AL137463, AL122110, AL137538, X70685, U35846, X96540, AL137271, U80742, AL133113, AL080127, U72620, A03736, I09360, AL080159, X93495, U67958, I26207, X98834, AC006336, A93350, I66342, I42402, AF061943, E15569, AJ012755, AL110197, AF000145, AL137521, AC004690, S61953, AF119337, AL133072, E08263, E08264, AF095901, AL050172, AR013797, I17767, U96683, Y09972, AL133568, AL110280, AC004093, AL133014, AF057300, AF057299, AR000496, U39656, AF026124, AL133104, AF111112, AL137523, I00734, AF008439, AL137526, AL122111, E00617, E00717, E00778, AL133098, AL137560, AL133077, AL122049, A08911, U68387, AL137556, A07647, AC006371, AF026816, AC004987, Y14314, E05822, AF109906, AF106827, M30514, Z37987, AC004686, AF003737, AJ006417, AL137476, AL122118, AR038969, U88966, AF079763, AC005940, AL133067, AR054984, AF091512, Z72491, AF162270, AF153205, U58996, AL117440, AF081197, AL137429, A90832, AF210052, A45787, AF185576, AF100931, AR038854, AC007390, AF111849, E04233, X62580, L30117, X83508, X87582, AL080074, AL117432, U49908, U62317, L13297, AL137533, and AC005992.
6	HEMFH17	7	1111071	AW300475, AA476679, AI202379, R84338, R93883, AA322984, AA766565, AL021917, AL050330, U90543,

				AR036564, U90142, U97495, U90550, and AR036568.
7	HSIDS22	8	1111073	AI991125, AA884903, AI339669, AW000848, and AB020625.

Table 3

		I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Met	1	A	.	.	.	.	.	.	-0.70	0.47	.	.	.	-0.40	0.41
Ala	2	A	.	.	.	.	.	.	-0.31	0.47	.	.	.	-0.40	0.32
Ser	3	A	.	.	.	.	.	.	-0.81	0.44	*	.	.	-0.40	0.43
Leu	4	A	.	.	B	.	.	.	-1.23	0.70	*	.	.	-0.60	0.31
Gly	5	A	.	.	B	.	.	.	-1.54	0.77	.	.	.	-0.60	0.25
Gln	6	.	.	B	B	.	.	.	-1.23	1.06	.	.	.	-0.60	0.16
Ile	7	.	.	B	B	.	.	.	-0.94	1.59	*	.	.	-0.60	0.21
Leu	8	.	.	B	B	.	.	.	-1.53	1.29	.	.	.	-0.60	0.28
Phe	9	.	.	B	B	.	.	.	-1.61	1.54	.	.	.	-0.60	0.11
Trp	10	.	.	B	B	.	.	.	-1.57	1.83	*	.	.	-0.60	0.11
Ser	11	.	.	B	B	.	.	.	-2.46	1.53	*	.	.	-0.60	0.18
Ile	12	.	.	B	B	.	.	.	-2.46	1.53	*	.	.	-0.60	0.15
Ile	13	.	.	B	B	.	.	.	-2.53	1.43	*	.	.	-0.60	0.10
Ser	14	.	.	B	B	.	.	.	-2.72	1.20	*	.	.	-0.60	0.05
Ile	15	.	.	B	B	.	.	.	-3.24	1.50	.	.	.	-0.60	0.05
Ile	16	.	.	B	B	.	.	.	-3.53	1.50	.	.	.	-0.60	0.06
Ile	17	.	.	B	B	.	.	.	-2.99	1.31	.	.	.	-0.60	0.05
Ile	18	.	.	B	B	.	.	.	-2.69	1.36	.	.	.	-0.60	0.07
Leu	19	.	.	B	B	.	.	.	-3.28	1.17	.	.	.	-0.60	0.09
Ala	20	A	.	.	B	.	.	.	-2.98	1.17	.	.	.	-0.60	0.09
Gly	21	A	.	.	B	.	.	.	-2.90	0.99	.	.	.	-0.60	0.14
Ala	22	A	.	.	B	.	.	.	-2.90	0.99	.	.	.	-0.60	0.14
Ile	23	A	.	.	B	.	.	.	-2.90	0.99	.	.	.	-0.60	0.09
Ala	24	.	.	B	B	.	.	.	-2.43	1.17	.	.	.	-0.60	0.07
Leu	25	.	.	B	B	.	.	.	-2.54	1.17	.	.	.	-0.60	0.07
Ile	26	.	.	B	B	.	.	.	-2.54	1.46	.	.	.	-0.60	0.08
Ile	27	.	.	B	B	.	.	.	-2.84	1.20	.	.	.	-0.60	0.08
Gly	28	.	.	B	B	.	.	.	-2.26	1.39	.	*	.	-0.60	0.07
Phe	29	.	.	B	B	.	.	.	-2.01	1.09	.	*	.	-0.60	0.13
Gly	30	.	.	B	B	.	.	.	-1.09	0.83	.	*	.	-0.60	0.18
Ile	31	.	.	.	B	.	.	C	-0.23	0.14	.	*	F	0.26	0.36
Ser	32	.	.	.	.	.	.	C	0.36	0.21	.	*	F	0.67	0.56
Gly	33	.	.	.	.	.	T	C	-0.19	-0.19	.	*	F	1.68	0.76
Arg	34	.	.	.	.	T	T	.	0.20	0.07	*	*	F	1.49	0.76
His	35	.	.	.	.	.	T	C	-0.31	-0.13	.	*	F	2.10	0.82
Ser	36	.	.	.	.	.	T	C	0.27	0.13	.	*	.	1.14	0.61
Ile	37	.	.	B	B	.	.	.	0.26	0.19	.	*	.	0.33	0.45
Thr	38	.	.	B	B	.	.	.	-0.26	0.67	*	*	.	-0.18	0.48
Val	39	.	.	B	B	.	.	.	-0.96	0.81	*	*	.	-0.39	0.27
Thr	40	.	.	B	B	.	.	.	-1.22	0.93	.	.	.	-0.60	0.38
Thr	41	.	.	B	B	.	.	.	-1.51	0.63	.	.	.	-0.60	0.36
Val	42	.	.	B	B	.	.	.	-0.97	0.64	.	.	.	-0.60	0.48
Ala	43	.	.	B	B	.	.	.	-0.66	0.43	.	.	.	-0.60	0.33
Ser	44	.	.	.	.	.	T	C	-0.69	0.34	*	.	.	0.30	0.37
Ala	45	.	.	B	.	.	T	C	-0.72	0.54	*	.	.	0.00	0.35
Gly	46	.	.	.	.	.	T	C	-0.41	0.33	*	.	F	0.45	0.34
Asn	47	.	.	.	.	.	T	C	0.44	-0.17	*	.	F	1.30	0.44
Ile	48	.	.	B	.	.	.	.	0.69	-0.56	*	.	F	1.45	0.73
Gly	49	.	.	B	.	.	T	.	0.10	-0.63	*	.	F	1.90	0.73
Glu	50	.	.	B	.	.	T	.	-0.12	-0.37	*	.	F	1.85	0.32
Asp	51	.	.	.	.	T	T	.	-0.08	-0.09	*	.	F	2.50	0.38
Gly	52	.	.	B	.	.	T	.	-0.74	-0.39	*	.	F	1.85	0.51
Ile	53	.	.	B	.	.	.	.	-0.17	-0.24	.	.	.	1.25	0.16
Leu	54	.	.	B	.	.	.	.	-0.52	0.24	.	.	.	0.40	0.14
Ser	55	.	.	B	.	.	.	.	-0.52	1.03	.	.	.	-0.15	0.12
Cys	56	.	.	B	.	.	.	.	-0.73	0.60	.	*	.	-0.40	0.29
Thr	57	.	.	B	.	.	.	.	-0.39	0.34	.	*	.	-0.10	0.55
Phe	58	.	.	B	.	.	.	.	-0.39	-0.34	*	*	.	0.50	0.69
Glu	59	A	.	B	.	.	T	.	0.47	-0.04	*	*	F	0.85	0.90
Pro	60	A	.	.	.	.	T	.	-0.04	-0.61	.	*	F	1.30	1.24
Asp	61	A	.	.	.	.	T	.	0.32	-0.41	*	*	F	1.00	1.19
Ile	62	A	.	.	.	.	T	.	0.63	-0.81	.	*	F	1.15	0.92
Lys	63	A	.	.	.	.	.	.	0.44	-0.81	*	*	F	0.95	0.99
Leu	64	A	.	.	B	.	.	.	-0.41	-0.56	*	*	F	0.75	0.42
Ser	65	A	.	.	B	.	.	.	-1.09	0.09	*	*	F	-0.15	0.44
Asp	66	A	.	.	B	.	.	.	-1.09	0.09	*	*	.	-0.30	0.15
Ile	67	.	.	B	B	.	.	.	-0.49	0.49	*	.	.	-0.60	0.32
Val	68	.	.	B	B	.	.	.	-1.34	0.71	*	.	.	-0.60	0.25

Ile	69	.	.	B	B	.	.	.	-0.49	1.01	*	.	.	-0.60	0.13
Gln	70	.	.	B	B	.	.	.	-0.19	1.01	*	.	.	-0.60	0.36
Trp	71	.	.	B	B	.	.	.	-0.53	0.33	*	.	.	-0.30	0.84
Leu	72	A	.	.	B	.	.	.	-0.50	0.11	*	.	.	-0.15	1.18
Lys	73	A	.	.	B	.	.	.	-0.46	0.07	*	.	F	-0.15	0.51
Glu	74	A	.	.	B	.	.	.	0.09	0.36	*	.	F	-0.15	0.40
Gly	75	.	.	.	B	T	.	.	-0.72	-0.13	*	.	F	0.85	0.48
Val	76	A	.	.	B	.	.	.	-1.29	-0.13	*	.	.	0.30	0.20
Leu	77	A	.	.	B	.	.	.	-0.51	0.51	*	.	.	-0.60	0.08
Gly	78	A	.	.	B	.	.	.	-0.56	1.01	*	.	.	-0.60	0.12
Leu	79	A	.	.	B	.	.	.	-1.26	0.59	*	.	.	-0.60	0.27
Val	80	A	.	.	B	.	.	.	-0.87	0.73	*	.	.	-0.60	0.28
His	81	A	.	.	B	.	.	.	-0.01	0.04	*	.	.	-0.30	0.57
Glu	82	A	A	.	.	.	.	.	0.46	-0.39	*	.	.	0.45	1.20
Phe	83	A	A	.	.	.	.	.	0.84	-0.64	*	.	.	0.75	1.60
Lys	84	A	A	.	.	.	.	.	1.66	-1.29	*	.	F	0.90	2.36
Glu	85	A	A	.	.	.	.	.	2.51	-1.79	*	.	F	0.90	2.27
Gly	86	A	.	.	.	.	T	.	1.73	-1.79	*	.	F	1.30	4.54
Lys	87	A	.	.	.	.	T	.	1.43	-1.89	*	.	F	1.30	1.87
Asp	88	A	.	.	.	.	T	.	2.13	-1.50	*	.	F	1.30	1.45
Glu	89	A	.	.	.	.	T	.	2.09	-1.50	*	.	F	1.30	2.54
Leu	90	A	A	.	.	.	.	.	2.09	-1.53	*	*	F	0.90	2.20
Ser	91	A	A	.	.	.	.	.	2.43	-1.53	*	.	F	0.90	2.20
Glu	92	A	A	.	.	.	.	.	1.79	-1.53	*	.	F	0.90	2.20
Gln	93	A	A	.	.	.	.	.	1.09	-0.91	*	.	F	0.90	2.64
Asp	94	A	A	.	.	.	.	.	1.20	-0.81	*	*	F	0.90	1.70
Glu	95	A	A	.	.	.	.	.	1.67	-1.20	.	*	F	0.90	1.93
Met	96	A	A	.	.	.	.	.	2.08	-0.77	.	*	.	0.75	1.10
Phe	97	A	.	.	.	.	T	.	1.77	-1.17	.	*	.	1.15	1.29
Arg	98	A	.	.	.	.	T	.	1.18	-0.69	*	*	F	1.30	1.08
Gly	99	A	.	.	.	.	T	.	0.32	-0.19	*	*	F	1.00	1.10
Arg	100	A	.	.	.	.	T	.	-0.38	-0.16	.	*	F	0.85	0.94
Thr	101	A	.	.	B	.	.	.	-0.37	-0.16	.	*	F	0.45	0.42
Ala	102	A	.	.	B	.	.	.	0.33	0.34	.	*	.	-0.30	0.43
Val	103	A	.	.	B	.	.	.	0.22	-0.09	.	*	.	0.30	0.36
Phe	104	.	.	B	B	.	.	.	-0.29	0.31	*	.	.	-0.30	0.43
Ala	105	.	.	B	B	.	.	.	-1.29	0.47	*	.	.	-0.60	0.32
Asp	106	.	.	B	B	.	.	.	-1.83	0.66	.	.	.	-0.60	0.30
Gln	107	.	.	B	B	.	.	.	-1.59	0.66	.	.	.	-0.60	0.26
Val	108	.	.	B	B	.	.	.	-0.73	0.30	.	.	.	-0.30	0.25
Ile	109	.	.	B	B	.	.	.	-0.62	0.20	.	.	.	-0.30	0.24
Val	110	.	.	B	B	.	.	.	-0.33	0.70	.	.	.	-0.60	0.14
Gly	111	.	.	B	B	.	.	.	-1.14	0.69	.	*	.	-0.60	0.26
Asn	112	.	.	B	.	.	T	.	-1.03	0.73	.	*	.	-0.20	0.30
Ala	113	A	.	.	.	.	T	.	-0.99	0.04	.	*	.	0.10	0.80
Ser	114	A	.	.	.	.	T	.	-0.06	0.09	*	*	.	0.10	0.66
Leu	115	A	.	.	.	.	T	.	0.80	-0.34	*	*	.	0.70	0.83
Arg	116	A	A	.	.	.	.	.	0.29	-0.34	.	*	.	0.45	1.32
Leu	117	.	A	B	.	.	.	.	0.29	-0.20	.	*	.	0.30	0.73
Lys	118	.	A	B	.	.	.	.	0.07	-0.19	.	*	.	0.45	1.53
Asn	119	.	A	B	.	.	.	.	0.06	-0.19	.	*	.	0.30	0.64
Val	120	.	A	B	.	.	.	.	0.87	0.30	.	*	.	-0.15	1.13
Gln	121	.	A	B	.	.	.	.	0.17	-0.39	.	.	.	0.30	0.94
Leu	122	.	A	B	.	.	.	.	0.63	0.11	.	.	.	-0.30	0.59
Thr	123	.	A	B	.	.	.	.	0.28	0.14	.	.	F	0.10	0.79
Asp	124	.	.	B	.	.	T	.	0.03	-0.01	.	*	F	1.35	0.66
Ala	125	.	.	.	.	T	T	.	0.93	0.34	.	.	F	1.55	1.25
Gly	126	.	.	.	.	T	T	.	0.27	-0.34	.	.	F	2.40	1.73
Thr	127	.	.	.	.	T	T	.	0.83	-0.26	.	.	F	2.50	0.56
Tyr	128	.	.	B	.	.	T	.	0.26	0.50	.	.	.	0.80	0.86
Lys	129	.	.	B	.	.	T	.	-0.63	0.69	.	.	.	0.55	0.61
Cys	130	.	.	B	.	.	T	.	-0.36	0.94	.	.	.	0.30	0.30
Tyr	131	.	.	B	.	.	T	.	-0.31	0.94	.	.	.	0.05	0.27
Ile	132	.	.	B	B	.	.	.	0.04	0.57	.	.	.	-0.26	0.18
Ile	133	.	.	B	B	.	.	.	-0.06	0.57	.	*	.	0.08	0.68
Thr	134	.	.	B	B	.	.	.	-0.06	0.43	.	*	F	0.57	0.43
Ser	135	.	.	B	.	.	T	.	0.27	-0.33	.	*	F	2.36	1.23
Lys	136	.	.	.	.	T	T	.	0.51	-0.59	.	*	F	3.40	1.74
Gly	137	.	.	.	.	T	T	.	0.81	-0.87	.	*	F	3.06	1.94
Lys	138	.	.	.	.	.	T	C	1.70	-0.86	*	*	F	2.52	1.46
Gly	139	.	.	.	.	.	.	C	1.20	-0.84	.	*	F	1.98	1.17
Asn	140	.	.	.	.	.	T	C	1.50	-0.16	.	*	F	1.39	0.98
Ala	141	.	.	B	.	.	T	.	1.21	-0.59	.	*	F	1.15	0.85

Asn	142	.	.	B	.	.	T	.	1.60	0.17	.	*	.	0.25	1.34
Leu	143	.	.	B	.	.	T	.	1.24	-0.26	.	*	.	0.85	1.67
Glu	144	.	.	B	.	.	.	.	1.24	-0.17	.	*	.	0.65	2.38
Tyr	145	A	.	.	.	.	T	.	0.66	-0.24	.	*	.	0.85	1.47
Lys	146	A	.	.	.	.	T	.	0.54	-0.14	.	*	F	1.00	1.79
Thr	147	A	.	.	.	.	T	.	0.24	-0.04	.	*	F	0.85	0.90
Gly	148	A	.	.	.	.	T	.	0.46	0.34	.	.	F	0.25	0.77
Ala	149	A	.	.	.	.	.	.	0.24	0.20	.	.	.	-0.10	0.38
Phe	150	.	.	B	.	.	.	.	0.49	0.63	*	.	.	-0.40	0.41
Ser	151	.	.	B	.	.	.	.	-0.41	0.14	.	.	.	-0.10	0.71
Met	152	.	.	B	.	.	.	.	-0.10	0.36	.	.	.	-0.10	0.52
Pro	153	.	.	B	.	.	.	.	-0.61	0.26	.	*	.	-0.10	0.97
Glu	154	.	.	B	.	.	.	.	-0.02	0.11	.	*	F	0.05	0.54
Val	155	A	.	.	.	.	.	.	0.43	-0.27	.	*	.	0.50	0.91
Asn	156	A	.	.	.	.	T	.	0.73	-0.13	.	*	.	0.70	0.92
Val	157	A	.	.	.	.	T	.	0.74	-0.16	.	*	.	0.70	0.85
Asp	158	A	.	.	.	.	T	.	0.66	0.34	.	*	.	0.25	1.16
Tyr	159	A	.	.	.	.	T	.	0.36	0.09	.	*	.	0.10	0.97
Asn	160	.	.	.	.	.	T	C	1.21	0.07	.	*	.	0.45	1.75
Ala	161	.	.	.	.	.	T	C	0.90	-0.57	.	*	F	1.50	1.81
Ser	162	A	.	.	.	.	T	.	0.94	-0.09	*	*	F	1.00	1.67
Ser	163	A	.	.	.	.	T	.	1.06	-0.16	*	*	F	0.85	0.86
Glu	164	A	A	.	.	.	.	.	0.63	-0.56	*	*	F	0.90	1.66
Thr	165	A	A	.	.	.	.	.	0.63	-0.49	*	*	F	0.45	0.66
Leu	166	.	A	B	.	.	.	.	0.63	-0.87	*	*	.	0.60	0.86
Arg	167	.	A	B	.	.	.	.	0.72	-0.76	*	.	.	0.76	0.50
Cys	168	.	A	B	.	.	.	.	1.13	-0.33	*	.	.	0.62	0.54
Glu	169	.	A	B	.	.	.	.	0.84	-0.81	*	.	.	1.23	1.28
Ala	170	.	.	.	.	.	T	C	0.46	-0.59	*	*	F	1.99	0.68
Pro	171	.	.	.	.	T	T	.	1.06	0.20	*	*	F	1.60	1.11
Arg	172	.	.	.	.	T	T	.	0.94	0.06	*	.	F	1.29	0.99
Trp	173	.	.	.	.	T	T	.	1.40	0.46	*	.	F	0.98	1.69
Phe	174	.	.	.	.	.	.	C	1.09	0.39	*	.	F	0.72	1.69
Pro	175	.	.	.	.	.	.	C	0.82	0.44	*	.	F	0.26	1.25
Gln	176	.	.	.	B	.	.	C	0.18	1.09	*	*	F	-0.25	0.88
Pro	177	.	.	.	B	.	.	C	-0.22	0.81	*	*	F	-0.25	0.75
Thr	178	.	.	.	B	.	.	C	-0.52	0.94	.	.	F	-0.25	0.51
Val	179	.	.	B	B	.	.	.	-0.12	1.01	.	.	.	-0.60	0.30
Val	180	.	.	B	B	.	.	.	0.09	1.00	.	.	.	-0.60	0.26
Trp	181	.	.	B	B	.	.	.	-0.77	0.97	.	.	.	-0.60	0.31
Ala	182	.	.	B	B	.	.	.	-0.56	1.13	.	.	.	-0.60	0.31
Ser	183	.	.	B	B	.	.	.	-0.24	0.49	.	.	.	-0.39	0.70
Gln	184	.	.	B	B	.	.	.	0.27	0.24	*	.	F	0.42	1.15
Val	185	.	.	B	B	.	.	.	0.53	-0.24	*	.	F	1.23	1.13
Asp	186	.	.	.	.	T	T	.	0.82	-0.24	*	*	F	2.09	0.85
Gln	187	.	.	.	.	.	T	C	0.71	-0.23	*	.	F	2.10	0.79
Gly	188	.	.	.	.	.	T	C	0.71	0.16	*	.	F	1.29	0.92
Ala	189	.	.	.	.	.	T	C	0.71	-0.10	*	.	F	1.68	0.74
Asn	190	.	.	.	.	.	.	C	0.71	-0.10	*	.	F	1.27	0.74
Phe	191	.	.	B	.	.	.	.	0.41	0.14	*	.	.	0.11	0.56
Ser	192	.	.	B	.	.	.	.	0.41	0.10	.	.	F	0.05	0.74
Glu	193	.	.	B	.	.	.	.	0.44	0.00	*	.	F	0.65	0.74
Val	194	.	.	B	.	.	.	.	0.73	0.09	*	.	F	0.20	1.23
Ser	195	.	.	.	.	.	.	C	0.03	-0.31	*	.	F	1.00	1.23
Asn	196	.	.	.	.	.	T	C	0.73	0.09	*	.	F	0.45	0.61
Thr	197	.	.	.	.	.	T	C	0.22	0.09	*	*	F	0.60	1.43
Ser	198	A	.	.	.	.	T	.	0.22	0.13	*	*	F	0.25	0.88
Phe	199	A	.	.	.	.	T	.	0.78	0.14	.	*	.	0.10	0.88
Glu	200	A	.	.	.	.	.	.	1.08	0.13	.	*	.	-0.10	0.82
Leu	201	A	.	.	.	.	.	.	1.08	-0.36	.	*	F	0.80	1.06
Asn	202	A	.	.	.	.	T	.	0.53	-0.34	.	*	F	1.00	1.97
Ser	203	A	.	.	.	.	T	.	0.52	-0.49	.	*	F	0.85	0.84
Glu	204	A	.	.	.	.	T	.	0.62	0.00	.	*	F	1.00	1.47
Asn	205	A	.	.	.	.	T	.	0.67	-0.07	.	*	F	0.85	0.91
Val	206	A	.	.	B	.	.	.	0.62	-0.47	*	.	F	0.60	1.35
Thr	207	A	.	.	B	.	.	.	-0.23	-0.21	*	.	.	0.30	0.58
Met	208	A	.	.	B	.	.	.	-0.23	0.43	*	.	.	-0.60	0.27
Lys	209	.	.	B	B	.	.	.	-1.09	0.41	*	.	.	-0.60	0.48
Val	210	.	.	B	B	.	.	.	-1.90	0.41	*	*	.	-0.60	0.25
Val	211	.	.	B	B	.	.	.	-1.29	0.61	*	.	.	-0.60	0.21
Ser	212	.	.	B	B	.	.	.	-0.98	0.76	*	.	.	-0.60	0.16
Val	213	.	.	B	B	.	.	.	-1.23	1.16	*	.	.	-0.60	0.35
Leu	214	.	.	B	B	.	.	.	-1.59	1.16	*	*	.	-0.60	0.35

Tyr	215	.	.	B	B	.	.	.	-1.62	1.00	*	*	.	-0.60	0.38
Asn	216	.	.	B	B	.	.	.	-0.77	1.30	.	*	.	-0.60	0.36
Val	217	.	.	B	B	.	.	.	-0.47	1.06	.	*	.	-0.60	0.70
Thr	218	.	.	B	B	.	.	.	0.08	0.77	.	*	.	-0.60	0.72
Ile	219	.	.	B	B	.	.	.	0.64	0.50	.	.	F	-0.45	0.64
Asn	220	.	.	.	B	T	.	.	0.59	0.86	.	*	F	0.10	1.36
Asn	221	.	.	.	.	T	T	.	-0.08	0.60	.	*	F	0.50	1.26
Thr	222	.	.	.	.	T	T	.	0.18	0.69	*	.	F	0.35	0.96
Tyr	223	.	.	B	.	.	T	.	-0.40	0.61	*	.	.	-0.20	0.59
Ser	224	.	.	B	.	.	T	.	0.49	0.90	*	.	.	-0.20	0.26
Cys	225	.	A	B	.	.	.	.	0.49	0.50	.	.	.	-0.60	0.31
Met	226	.	A	B	.	.	.	.	0.49	0.41	*	*	.	-0.60	0.32
Ile	227	.	A	B	.	.	.	.	-0.09	-0.34	.	.	.	0.30	0.40
Glu	228	A	A	.	.	.	.	.	-0.43	-0.04	*	.	.	0.30	0.52
Asn	229	A	A	.	.	.	.	.	-0.09	-0.11	*	.	F	0.45	0.53
Asp	230	A	A	.	.	.	.	.	-0.01	-0.73	*	.	F	0.90	1.51
Ile	231	A	A	.	.	.	.	.	0.28	-0.91	*	.	F	0.75	0.88
Ala	232	A	A	.	.	.	.	.	0.82	-0.43	*	.	F	0.45	0.79
Lys	233	A	A	.	.	.	.	.	0.82	-0.40	*	*	F	0.45	0.47
Ala	234	A	.	.	.	.	T	.	-0.07	-0.40	*	*	F	1.00	1.12
Thr	235	A	.	.	.	.	T	.	-0.02	-0.40	*	*	F	0.85	0.77
Gly	236	A	.	.	.	.	T	.	0.01	-0.90	*	*	F	1.15	0.77
Asp	237	A	.	.	.	.	T	.	0.29	-0.26	.	*	F	0.85	0.57
Ile	238	A	.	.	B	.	.	.	0.24	-0.27	.	*	F	0.45	0.57
Lys	239	A	.	.	B	.	.	.	0.53	-0.76	.	*	F	0.75	1.00
Val	240	A	.	.	B	.	.	.	0.84	-0.80	.	*	F	0.75	0.80
Thr	241	A	A	.	B	.	.	.	0.30	-0.80	*	*	F	0.90	1.97
Glu	242	A	A	.	B	.	.	.	0.34	-0.80	*	*	F	0.75	0.69
Ser	243	A	A	.	.	.	.	.	1.34	-0.80	*	*	F	0.90	1.86
Glu	244	A	A	.	.	.	.	.	1.41	-1.44	*	.	F	0.90	2.53
Ile	245	A	A	.	.	.	.	.	1.97	-1.93	.	*	F	0.90	2.86
Lys	246	A	A	.	.	.	.	.	2.24	-1.54	.	*	F	0.90	2.86
Arg	247	A	A	.	.	.	.	.	1.43	-1.43	.	*	F	0.90	2.25
Arg	248	A	A	.	.	.	.	.	1.73	-0.74	*	*	F	0.90	2.64
Ser	249	A	A	.	.	.	.	.	0.92	-1.03	*	*	F	0.90	2.29
His	250	A	A	.	.	.	.	.	1.00	-0.34	.	*	.	0.30	0.96
Leu	251	A	A	.	.	.	.	.	0.96	0.34	*	.	.	-0.30	0.41
Gln	252	.	A	B	.	.	.	.	0.54	0.74	*	.	.	-0.60	0.49
Leu	253	.	A	B	.	.	.	.	0.48	0.74	*	*	.	-0.60	0.48
Leu	254	.	A	B	.	.	.	.	0.19	0.24	.	.	.	-0.15	1.16
Asn	255	.	.	.	.	T	T	.	-0.08	0.06	.	*	F	0.65	0.68
Ser	256	.	.	.	.	T	T	.	-0.08	0.04	.	*	F	0.80	1.10
Lys	257	A	.	.	.	.	T	.	-0.74	0.04	.	*	F	0.40	1.10
Ala	258	.	.	B	.	.	T	.	-0.79	-0.07	.	*	F	0.85	0.37
Ser	259	.	.	B	B	.	.	.	-0.28	0.17	.	*	.	-0.30	0.20
Leu	260	.	.	B	B	.	.	.	-0.58	0.17	.	*	.	-0.30	0.14
Cys	261	.	.	B	B	.	.	.	-0.98	0.56	*	*	.	-0.60	0.18
Val	262	.	.	B	B	.	.	.	-1.72	0.84	*	*	.	-0.60	0.12
Ser	263	.	.	B	B	.	.	.	-1.72	1.24	.	.	.	-0.60	0.12
Ser	264	.	.	B	B	.	.	.	-2.31	1.06	.	.	.	-0.60	0.23
Phe	265	.	.	B	B	.	.	.	-1.80	1.17	.	.	.	-0.60	0.22
Phe	266	.	.	B	B	.	.	.	-1.42	0.91	.	.	.	-0.60	0.22
Ala	267	A	.	.	B	.	.	.	-1.16	1.44	.	.	.	-0.60	0.17
Ile	268	A	.	.	B	.	.	.	-1.67	1.56	.	.	.	-0.60	0.20
Ser	269	A	.	.	B	.	.	.	-2.18	1.46	.	.	.	-0.60	0.19
Trp	270	A	.	.	B	.	.	.	-1.69	1.36	.	.	.	-0.60	0.16
Ala	271	A	.	.	B	.	.	.	-1.80	1.29	.	.	.	-0.60	0.34
Leu	272	.	.	.	B	.	.	C	-1.51	1.29	.	.	.	-0.40	0.21
Leu	273	.	.	.	B	.	.	C	-0.83	1.29	.	.	.	-0.40	0.27
Pro	274	.	.	.	B	.	.	C	-0.78	0.80	.	.	.	-0.40	0.41
Leu	275	.	.	.	.	.	.	C	-1.30	1.06	.	.	.	-0.20	0.78
Ser	276	.	.	.	.	.	T	C	-1.31	1.06	.	.	.	0.00	0.78
Pro	277	A	.	.	.	.	T	.	-1.31	0.99	.	*	.	-0.20	0.50
Tyr	278	A	.	.	.	.	T	.	-0.46	1.24	.	*	.	-0.20	0.50
Leu	279	A	.	.	.	.	T	.	-0.63	0.56	.	*	.	-0.20	0.75
Met	280	A	.	.	.	.	.	.	-0.21	0.60	.	*	.	-0.40	0.62
Leu	281	.	.	B	.	.	.	.	-0.30	0.60	.	.	.	-0.40	0.50
Lys	282	.	.	B	.	.	.	.	-0.48	0.27	.	.	.	-0.10	0.78

Table 4

		I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Met	1	A	A	.	.	.	.	.	-1.87	1.06	.	.	.	-0.60	0.19
Ile	2	A	A	.	.	.	.	.	-2.29	1.31	.	.	.	-0.60	0.12
Phe	3	A	A	.	.	.	.	.	-2.50	1.57	.	.	.	-0.60	0.08
Leu	4	A	A	.	.	.	.	.	-2.92	1.76	.	.	.	-0.60	0.08
Leu	5	A	A	.	.	.	.	.	-2.83	1.83	.	.	.	-0.60	0.09
Leu	6	A	A	.	.	.	.	.	-3.04	1.53	.	.	.	-0.60	0.14
Met	7	A	A	.	.	.	.	.	-2.16	1.43	.	*	.	-0.60	0.14
Leu	8	A	A	.	.	.	.	.	-2.27	0.74	.	*	.	-0.60	0.30
Ser	9	A	A	.	.	.	.	.	-1.46	0.74	.	*	.	-0.60	0.30
Leu	10	A	A	.	.	.	.	.	-1.46	0.46	.	*	.	-0.60	0.52
Glu	11	A	A	.	.	.	.	.	-0.68	0.53	.	*	.	-0.60	0.52
Leu	12	A	A	.	.	.	.	.	-0.08	0.34	.	*	.	-0.30	0.52
Gln	13	A	A	.	.	.	.	.	-0.16	0.36	.	*	.	-0.15	1.10
Leu	14	A	A	.	.	.	.	.	-0.44	0.36	.	*	.	-0.30	0.45
His	15	A	A	.	.	.	.	.	-0.22	0.86	.	*	.	-0.60	0.55
Gln	16	A	A	.	.	.	.	.	-1.03	0.67	.	.	.	-0.60	0.32
Ile	17	A	A	.	.	.	.	.	-0.92	0.96	.	.	.	-0.60	0.32
Ala	18	A	A	.	.	.	.	.	-1.23	1.06	*	.	.	-0.60	0.20
Ala	19	A	A	.	.	.	.	.	-1.28	1.04	*	.	.	-0.60	0.17
Leu	20	.	A	B	.	.	.	.	-1.56	1.29	*	*	.	-0.60	0.18
Phe	21	.	A	B	.	.	.	.	-2.41	1.09	.	*	.	-0.60	0.26
Thr	22	.	A	B	.	.	.	.	-1.73	1.23	.	.	.	-0.60	0.19
Val	23	.	A	B	.	.	.	.	-1.10	1.16	.	.	.	-0.60	0.35
Thr	24	.	A	B	.	.	.	.	-0.51	0.47	.	.	.	-0.60	0.81
Val	25	.	A	.	.	.	.	C	-0.51	-0.31	.	.	F	0.65	0.98
Pro	26	A	.	.	.	.	.	.	-0.06	-0.11	.	*	F	0.80	1.08
Lys	27	A	.	.	.	.	.	.	-0.63	0.00	.	.	F	0.80	1.18
Glu	28	A	.	.	B	.	.	.	-0.67	0.20	.	.	F	0.00	1.11
Leu	29	A	.	.	B	.	.	.	-0.36	0.24	*	.	.	-0.30	0.50
Tyr	30	.	.	B	B	.	.	.	0.47	-0.19	*	.	.	0.30	0.44
Ile	31	.	.	B	B	.	.	.	0.33	0.31	*	.	.	-0.30	0.34
Ile	32	.	.	B	B	.	.	.	-0.01	0.74	*	.	.	-0.60	0.41
Glu	33	A	.	.	B	.	.	.	-0.01	0.44	*	.	.	-0.60	0.35
His	34	.	.	.	.	T	.	.	-0.06	0.09	*	.	.	0.30	0.81
Gly	35	.	.	.	.	T	T	.	-0.12	0.04	*	.	F	0.65	0.86
Ser	36	.	.	.	.	.	T	C	-0.04	-0.16	*	*	F	1.05	0.71
Asn	37	.	.	.	.	.	T	C	0.84	0.53	*	*	F	0.15	0.43
Val	38	.	.	.	.	.	T	C	0.18	0.03	.	*	.	0.30	0.76
Thr	39	.	.	B	.	.	.	.	0.21	0.17	.	*	.	0.08	0.30
Leu	40	.	.	B	.	.	.	.	-0.14	0.19	.	*	.	0.26	0.30
Glu	41	.	.	B	.	.	.	.	0.16	0.57	.	*	.	0.14	0.35
Cys	42	.	.	B	.	.	.	.	-0.16	-0.07	.	*	.	1.22	0.41
Asn	43	.	.	B	.	T	.	.	0.36	-0.07	.	*	.	1.80	0.71
Phe	44	.	.	.	.	T	.	.	0.37	-0.33	*	*	.	1.62	0.41
Asp	45	.	.	.	.	T	T	.	1.14	0.06	*	*	F	1.26	1.02
Thr	46	.	.	.	.	T	T	.	0.29	-0.01	.	*	F	1.45	0.86
Gly	47	.	.	.	.	T	T	.	0.96	0.23	.	*	F	0.59	0.74
Ser	48	.	.	.	.	.	T	C	0.14	-0.16	.	*	F	0.73	0.71
His	49	.	.	B	.	.	.	.	0.50	0.53	.	*	.	-0.80	0.41
Val	50	.	.	B	.	.	.	.	-0.09	0.47	.	.	.	-0.72	0.41
Asn	51	.	.	B	.	.	.	.	-0.67	0.54	.	.	.	-0.64	0.31
Leu	52	.	.	B	.	.	.	.	-0.63	0.84	.	.	.	-0.56	0.16
Gly	53	.	.	B	.	.	.	.	-0.92	0.83	.	.	.	-0.48	0.31
Ala	54	.	.	B	.	.	.	.	-1.19	0.69	.	*	.	-0.40	0.19
Ile	55	A	.	.	.	.	.	.	-1.14	0.67	.	*	.	-0.40	0.31
Thr	56	A	A	.	.	.	.	.	-1.14	0.67	*	.	.	-0.60	0.26
Ala	57	A	A	.	.	.	.	.	-0.29	0.64	*	.	.	-0.60	0.45
Ser	58	A	A	.	.	.	.	.	-0.80	0.14	*	.	.	-0.15	1.28
Leu	59	A	A	.	.	.	.	.	-0.21	0.10	*	.	.	-0.30	0.66
Gln	60	.	A	B	.	.	.	.	0.68	-0.39	*	.	F	0.60	1.13
Lys	61	.	A	B	.	.	.	.	0.99	-0.49	*	.	F	0.90	1.35
Val	62	.	A	B	.	.	.	.	1.27	-0.87	*	.	F	1.50	2.74
Glu	63	.	A	B	.	.	.	.	1.27	-1.07	*	.	F	1.80	2.28
Asn	64	.	A	.	.	T	.	.	1.87	-1.09	*	.	F	2.50	1.53
Asp	65	.	.	.	.	T	.	.	1.83	-0.66	.	.	F	3.00	3.19
Thr	66	.	.	.	.	.	.	C	1.90	-0.80	.	*	F	2.50	2.51
Ser	67	.	.	.	.	.	T	C	2.76	-0.80	.	*	F	2.40	3.05
Pro	68	.	.	.	.	.	T	C	2.87	-1.20	.	*	F	2.10	3.16
His	69	A	.	.	.	.	T	.	2.28	-1.20	.	*	F	1.60	4.29
Arg	70	A	.	.	.	.	T	.	1.97	-1.19	.	*	F	1.30	3.24

Glu	71	A	A	.	.	.	.	.	1.47	-1.09	.	*	F	0.90	3.02
Arg	72	A	A	.	.	.	.	.	0.96	-0.83	.	*	F	0.90	1.83
Ala	73	A	A	.	.	.	.	.	1.17	-0.64	.	*	F	0.75	0.77
Thr	74	A	A	.	.	.	.	.	1.20	-0.64	.	*	.	0.60	0.77
Leu	75	A	A	.	.	.	.	.	1.09	-0.64	.	*	.	0.60	0.68
Leu	76	A	A	.	.	.	.	.	0.28	-0.24	*	.	.	0.45	1.17
Glu	77	A	A	.	.	.	.	.	-0.04	-0.06	.	*	F	0.45	0.67
Glu	78	A	A	.	.	.	.	.	-0.27	-0.11	.	.	F	0.60	1.25
Gln	79	A	A	.	.	.	.	.	-0.30	-0.11	*	.	F	0.60	1.25
Leu	80	A	.	.	.	.	T	.	0.56	-0.37	*	.	.	0.70	0.72
Pro	81	A	.	.	.	.	T	.	0.78	-0.37	.	.	.	0.70	0.83
Leu	82	A	.	.	.	.	T	.	0.48	0.13	.	.	.	0.10	0.48
Gly	83	A	.	.	.	.	T	.	-0.22	0.11	.	.	F	0.25	0.78
Lys	84	A	.	.	.	.	.	.	-0.26	0.21	.	*	F	0.05	0.44
Ala	85	A	.	.	.	.	.	.	-0.33	0.29	*	*	.	-0.10	0.72
Ser	86	.	.	B	B	.	.	.	-0.33	0.29	*	*	.	-0.30	0.51
Phe	87	.	.	B	B	.	.	.	0.48	0.29	*	*	.	-0.30	0.40
His	88	.	.	B	B	.	.	.	-0.03	0.69	.	*	.	-0.60	0.68
Ile	89	.	.	B	B	.	.	.	-0.08	0.83	.	*	.	-0.60	0.38
Pro	90	.	.	B	B	.	.	.	-0.34	0.84	*	*	.	-0.60	0.75
Gln	91	.	.	B	B	.	.	.	0.07	0.70	*	*	.	-0.60	0.41
Val	92	.	.	B	B	.	.	.	0.77	0.20	.	*	.	-0.15	1.15
Gln	93	.	.	B	B	.	.	.	0.80	-0.49	.	*	.	0.79	1.24
Val	94	.	.	B	B	.	.	.	1.34	-0.91	.	*	.	1.43	1.24
Arg	95	.	.	B	B	.	.	.	1.56	-0.89	.	*	F	1.92	1.65
Asp	96	.	.	.	.	T	T	.	1.31	-1.13	.	*	F	3.06	1.65
Glu	97	.	.	.	.	T	T	.	2.17	-0.77	.	*	F	3.40	3.49
Gly	98	.	.	.	.	T	T	.	1.50	-1.01	.	*	F	3.06	3.08
Gln	99	.	.	.	.	T	T	.	1.47	-0.44	*	*	F	2.27	0.99
Tyr	100	.	.	B	B	.	.	.	0.47	0.24	*	*	.	0.38	0.40
Gln	101	.	.	B	B	.	.	.	-0.42	0.93	.	.	.	-0.26	0.28
Cys	102	.	.	B	B	.	.	.	-0.67	1.19	.	.	.	-0.60	0.11
Ile	103	.	.	B	B	.	.	.	-0.67	1.54	.	.	.	-0.60	0.11
Ile	104	.	.	B	B	.	.	.	-1.52	1.21	.	.	.	-0.60	0.07
Ile	105	.	.	B	B	.	.	.	-1.87	1.46	.	.	.	-0.60	0.09
Tyr	106	.	.	B	B	.	.	.	-2.16	1.39	.	.	.	-0.60	0.13
Gly	107	.	.	B	B	.	.	.	-1.49	1.61	.	.	.	-0.60	0.20
Val	108	.	.	B	B	.	.	.	-0.84	0.93	.	*	.	-0.60	0.47
Ala	109	.	.	B	B	.	.	.	0.09	1.00	.	*	.	-0.60	0.47
Trp	110	.	.	.	.	T	T	.	0.73	0.24	.	.	.	0.50	0.95
Asp	111	A	.	.	.	.	T	.	0.17	0.57	.	.	.	-0.05	2.00
Tyr	112	A	.	.	.	.	T	.	0.20	0.61	.	.	.	-0.05	1.63
Lys	113	A	.	.	.	.	T	.	0.24	0.60	.	*	.	-0.05	2.24
Tyr	114	A	.	.	B	.	.	.	0.88	0.37	.	*	.	-0.15	1.10
Leu	115	A	.	.	B	.	.	.	0.31	0.37	.	*	.	-0.15	1.41
Thr	116	A	.	.	B	.	.	.	0.36	0.26	.	*	.	-0.30	0.52
Leu	117	A	.	.	B	.	.	.	0.01	0.26	.	*	.	-0.30	0.67
Lys	118	A	.	.	B	.	.	.	-0.33	0.00	.	*	F	0.45	0.82
Val	119	A	.	.	B	.	.	.	-0.33	-0.30	*	*	F	0.45	0.76
Lys	120	A	.	.	B	.	.	.	0.59	-0.03	*	*	F	0.60	1.44
Ala	121	A	.	.	.	.	T	.	0.94	-0.71	*	*	F	1.30	1.41
Ser	122	A	.	.	.	.	T	.	0.87	-0.71	*	*	.	1.15	3.81
Tyr	123	A	.	.	.	.	T	.	0.82	-0.67	*	*	F	1.30	1.34
Arg	124	A	.	.	.	.	T	.	1.37	-0.27	*	*	F	1.00	2.13
Lys	125	A	.	.	B	.	.	.	1.29	-0.29	*	*	F	0.60	2.29
Ile	126	.	.	B	B	.	.	.	0.99	-0.17	*	.	F	0.60	1.99
Asn	127	.	.	B	B	.	.	.	0.48	-0.24	*	.	F	0.45	0.71
Thr	128	.	.	B	B	.	.	.	0.77	0.44	*	.	.	-0.60	0.29
His	129	.	.	B	B	.	.	.	-0.20	0.44	*	.	.	-0.60	0.84
Ile	130	.	.	B	B	.	.	.	-0.46	0.40	*	*	.	-0.30	0.39
Leu	131	.	.	B	B	.	.	.	0.43	0.43	*	.	.	-0.60	0.41
Lys	132	.	.	B	B	.	.	.	0.12	-0.06	*	.	F	0.45	0.53
Val	133	.	.	B	B	.	.	.	0.43	-0.07	*	.	F	0.60	1.08
Pro	134	.	.	.	.	.	.	C	0.47	-0.76	.	.	F	1.30	2.20
Glu	135	A	A	.	.	.	.	.	0.50	-1.44	.	.	F	0.90	1.90
Thr	136	A	A	.	.	.	.	.	1.31	-0.80	.	*	F	0.90	1.90
Asp	137	A	A	.	.	.	.	.	0.46	-1.44	.	*	F	0.90	2.13
Glu	138	A	A	.	.	.	.	.	1.00	-1.19	.	.	F	0.90	1.01
Val	139	A	A	.	.	.	.	.	0.54	-0.70	.	*	.	0.75	1.01
Glu	140	A	A	.	.	.	.	.	0.54	-0.61	.	*	.	0.60	0.33
Leu	141	A	A	.	.	.	.	.	0.27	-0.21	.	*	.	0.30	0.33
Thr	142	A	A	.	.	.	.	.	-0.04	0.29	.	*	.	-0.30	0.44
Cys	143	A	A	.	.	.	.	.	-0.39	0.13	.	*	.	-0.30	0.37

Gln	144	A	A	.	.	.	.	.	0.22	0.56	.	*	.	-0.60	0.44
Ala	145	.	.	.	.	T	T	.	0.01	0.63	.	*	.	0.20	0.48
Thr	146	.	.	.	.	T	T	.	0.01	0.57	.	.	F	0.50	1.39
Gly	147	.	.	.	.	.	T	C	-0.27	0.69	.	.	.	0.00	0.66
Tyr	148	.	.	B	.	.	T	.	0.40	0.79	*	.	.	-0.20	0.66
Pro	149	.	A	B	.	.	.	.	-0.46	0.29	.	.	.	-0.30	0.79
Leu	150	.	A	B	.	.	.	.	-0.17	0.44	.	.	.	-0.60	0.59
Ala	151	.	A	B	.	.	.	.	-0.14	0.40	.	.	.	-0.30	0.51
Glu	152	.	A	B	.	.	.	.	-0.01	0.56	.	.	.	-0.60	0.35
Val	153	.	A	B	.	.	.	.	0.23	0.56	.	.	.	-0.60	0.65
Ser	154	.	A	B	.	.	.	.	-0.41	0.27	.	.	.	-0.15	1.03
Trp	155	.	.	.	.	.	T	C	0.10	0.41	.	.	.	0.00	0.44
Pro	156	.	.	.	.	.	T	C	-0.17	0.80	.	.	.	0.00	0.80
Asn	157	.	.	.	.	T	T	.	-0.38	0.80	.	.	.	0.20	0.44
Val	158	.	.	B	.	.	T	.	-0.11	0.84	.	*	.	-0.20	0.65
Ser	159	.	.	B	.	.	.	.	0.19	0.43	.	*	.	-0.40	0.43
Val	160	.	.	B	.	.	.	.	0.17	0.40	.	*	.	-0.10	0.43
Pro	161	.	.	B	.	.	T	.	0.08	0.49	.	*	.	-0.20	0.83
Ala	162	.	.	.	.	T	T	.	0.04	0.23	.	*	F	0.65	0.83
Asn	163	.	.	.	.	.	T	C	0.60	0.34	.	*	F	0.60	1.52
Thr	164	.	.	B	.	.	T	.	1.01	0.09	.	.	F	0.40	1.31
Ser	165	.	.	.	.	.	.	C	1.56	-0.34	.	.	F	1.00	2.55
His	166	.	.	.	.	.	.	C	1.56	-0.36	*	.	F	1.34	2.29
Ser	167	.	.	.	.	.	.	C	2.14	-0.33	*	.	F	1.68	2.45
Arg	168	.	.	.	.	.	.	C	1.80	-0.81	*	.	F	2.32	3.16
Thr	169	.	.	.	.	.	T	C	1.30	-0.77	*	.	F	2.86	2.30
Pro	170	.	.	.	.	T	T	.	1.36	-0.59	*	.	F	3.40	1.42
Glu	171	.	.	.	.	T	T	.	1.39	-0.21	*	.	F	2.76	1.13
Gly	172	.	.	B	.	.	T	.	0.83	0.19	*	.	F	1.42	1.36
Leu	173	.	.	B	B	.	.	.	0.41	0.34	*	.	.	0.38	0.65
Tyr	174	.	.	B	B	.	.	.	0.42	0.40	*	.	.	0.04	0.54
Gln	175	.	.	B	B	.	.	.	-0.22	0.79	*	.	.	-0.60	0.74
Val	176	.	.	B	B	.	.	.	-1.03	1.00	*	*	.	-0.60	0.66
Thr	177	.	.	B	B	.	.	.	-0.58	1.00	*	*	.	-0.60	0.35
Ser	178	.	.	B	B	.	.	.	-0.58	0.24	*	*	.	-0.30	0.39
Val	179	.	.	B	B	.	.	.	-0.29	0.53	*	*	.	-0.60	0.44
Leu	180	.	.	B	B	.	.	.	-0.50	-0.11	*	*	.	0.30	0.61
Arg	181	.	.	B	B	.	.	.	0.14	-0.17	*	*	.	0.30	0.70
Leu	182	.	.	B	B	.	.	.	0.24	-0.13	*	*	.	0.79	1.46
Lys	183	.	.	B	B	.	.	.	0.20	-0.34	*	*	F	1.28	2.74
Pro	184	.	.	.	.	.	.	C	1.17	-0.60	*	*	F	2.32	1.38
Pro	185	.	.	.	.	.	T	C	1.98	-0.60	*	*	F	2.86	3.29
Pro	186	.	.	.	.	T	T	.	1.17	-0.89	*	*	F	3.40	2.64
Gly	187	.	.	.	.	T	T	.	1.68	-0.10	*	.	F	2.76	1.48
Arg	188	.	.	.	.	T	T	.	0.97	-0.14	*	.	F	2.42	1.28
Asn	189	.	.	B	.	.	T	.	0.32	0.00	*	.	.	1.38	0.44
Phe	190	.	.	B	.	.	T	.	-0.17	0.21	*	.	.	0.44	0.33
Ser	191	.	.	B	.	.	T	.	-0.24	0.57	*	.	.	-0.20	0.15
Cys	192	.	.	B	.	.	T	.	0.10	1.49	*	.	.	-0.20	0.10
Val	193	.	.	B	B	.	.	.	-0.32	1.49	*	.	.	-0.60	0.18
Phe	194	.	.	.	B	T	.	.	-0.36	1.19	.	.	.	-0.20	0.19
Trp	195	.	.	.	B	T	.	.	-0.51	1.30	*	*	.	-0.20	0.49
Asn	196	.	.	.	B	.	.	C	-0.10	1.37	*	*	.	-0.40	0.49
Thr	197	.	.	.	B	.	.	C	0.57	0.73	*	*	.	-0.25	1.11
His	198	.	A	.	.	.	.	C	0.61	-0.06	*	*	.	0.65	1.82
Val	199	A	A	.	.	.	.	.	1.00	-0.29	*	.	.	0.30	0.93
Arg	200	A	A	.	.	.	.	.	0.48	-0.20	*	*	.	0.30	0.93
Glu	201	A	A	.	.	.	.	.	-0.11	0.00	*	.	.	0.30	0.57
Leu	202	A	A	.	.	.	.	.	-0.10	0.00	.	.	.	0.30	0.77
Thr	203	A	A	.	.	.	.	.	-0.96	-0.26	*	.	.	0.30	0.53
Leu	204	A	A	.	.	.	.	.	-0.10	0.43	*	*	.	-0.60	0.21
Ala	205	A	A	.	.	.	.	.	-1.02	0.43	*	*	.	-0.60	0.43
Ser	206	A	A	.	.	.	.	.	-1.02	0.43	.	*	.	-0.60	0.25
Ile	207	A	A	.	.	.	.	.	-0.51	0.34	.	*	.	-0.30	0.52
Asp	208	A	A	.	.	.	.	.	-0.20	0.04	.	*	.	-0.30	0.69
Leu	209	A	A	.	.	.	.	.	0.01	-0.06	.	*	F	0.45	0.89
Gln	210	A	A	.	.	.	.	.	0.60	0.17	.	*	F	0.00	1.26
Ser	211	.	A	.	.	.	.	C	0.69	-0.51	.	*	F	1.44	1.30
Gln	212	.	A	B	.	.	.	.	1.69	-0.09	*	*	F	1.28	2.44
Met	213	.	A	.	.	.	.	C	1.38	-0.77	.	*	F	2.12	2.76
Glu	214	.	.	B	.	.	T	.	2.16	-0.69	.	*	F	2.66	2.97
Pro	215	.	.	.	.	T	T	.	1.94	-0.57	.	*	F	3.40	2.34
Arg	216	.	.	.	.	T	T	.	1.93	-0.54	*	*	F	3.06	3.65

Thr	217	.	.	.	.	.	T	C	1.64	-0.67	*	*	F	2.52	3.04
His	218	.	.	.	.	.	T	C	1.43	0.24	.	*	F	1.28	2.07
Pro	219	.	.	.	.	.	T	C	0.62	0.50	.	*	F	0.49	0.87
Thr	220	.	.	.	.	T	T	.	0.80	1.19	*	*	.	0.20	0.50
Trp	221	A	.	.	.	.	T	.	-0.20	1.20	*	*	.	-0.20	0.50
Leu	222	.	.	B	B	.	.	.	-0.59	1.39	.	.	.	-0.60	0.23
Leu	223	.	.	B	B	.	.	.	-1.44	1.74	.	.	.	-0.60	0.14
His	224	.	.	B	B	.	.	.	-1.44	1.94	.	.	.	-0.60	0.09
Ile	225	.	.	B	B	.	.	.	-1.43	1.46	.	.	.	-0.60	0.17
Phe	226	.	.	B	B	.	.	.	-1.81	1.16	.	.	.	-0.60	0.28
Ile	227	.	.	B	.	.	T	.	-1.89	1.04	.	.	.	-0.20	0.11
Pro	228	.	.	.	.	T	T	.	-1.97	1.23	.	.	.	0.20	0.11
Ser	229	.	.	.	.	T	T	.	-2.52	1.23	.	.	.	0.20	0.09
Cys	230	.	.	B	.	.	T	.	-2.33	0.94	.	.	.	-0.20	0.13
Ile	231	.	.	B	B	.	.	.	-2.52	1.04	.	.	.	-0.60	0.07
Ile	232	.	.	B	B	.	.	.	-2.33	1.30	.	.	.	-0.60	0.04
Ala	233	.	.	B	B	.	.	.	-3.01	1.70	.	.	.	-0.60	0.06
Phe	234	.	.	B	B	.	.	.	-3.30	1.81	.	.	.	-0.60	0.06
Ile	235	.	.	B	B	.	.	.	-2.94	1.63	.	.	.	-0.60	0.09
Phe	236	.	.	B	B	.	.	.	-2.91	1.43	.	.	.	-0.60	0.12
Ile	237	A	.	.	B	.	.	.	-2.91	1.57	.	.	.	-0.60	0.11
Ala	238	A	.	.	B	.	.	.	-2.91	1.47	.	.	.	-0.60	0.11
Thr	239	A	.	.	B	.	.	.	-3.02	1.29	.	*	.	-0.60	0.12
Val	240	A	.	.	B	.	.	.	-2.02	1.19	*	.	.	-0.60	0.14
Ile	241	A	.	.	B	.	.	.	-1.28	0.50	.	.	.	-0.60	0.28
Ala	242	A	.	.	B	.	.	.	-0.39	0.00	.	*	.	0.30	0.39
Leu	243	A	.	.	B	.	.	.	-0.61	-0.09	.	*	.	0.30	0.91
Arg	244	A	.	.	B	.	.	.	-0.97	-0.04	*	.	.	0.45	1.07
Lys	245	A	.	.	B	.	.	.	-0.11	-0.16	.	*	F	0.45	0.57
Gln	246	A	A	.	.	.	.	.	0.82	-0.26	.	*	F	0.60	1.19
Leu	247	A	A	.	.	.	.	.	0.60	-0.94	.	*	.	0.75	1.22
Cys	248	.	A	B	.	.	.	.	1.17	-0.26	*	*	.	0.30	0.50
Gln	249	.	A	B	.	.	.	.	0.76	0.50	.	*	.	-0.60	0.45
Lys	250	.	A	B	.	.	.	.	0.41	0.49	*	.	.	-0.60	0.74
Leu	251	.	A	B	.	.	.	.	0.46	0.19	*	.	F	0.34	1.84
Tyr	252	.	A	B	.	.	.	.	1.27	-0.39	*	.	F	1.28	2.13
Ser	253	.	.	.	.	T	.	.	1.62	-0.79	.	.	F	2.52	1.78
Ser	254	.	.	.	.	T	T	.	1.31	-0.30	.	.	F	2.76	3.11
Lys	255	.	.	.	.	T	T	.	1.31	-0.50	*	.	F	3.40	2.86
Asp	256	.	.	.	.	T	T	.	2.23	-1.26	*	.	F	3.06	4.27
Thr	257	.	.	.	.	T	T	.	2.27	-1.64	*	.	F	2.72	6.25
Thr	258	.	.	B	.	.	.	.	1.71	-1.60	*	.	F	1.78	4.83
Lys	259	.	.	B	.	.	.	.	1.70	-0.96	*	.	F	1.44	2.15
Arg	260	.	.	B	B	.	.	.	1.34	-0.47	*	.	F	0.60	2.15
Pro	261	.	.	B	B	.	.	.	1.03	-0.47	*	.	F	0.60	2.15
Val	262	.	.	B	B	.	.	.	1.39	-0.47	*	.	F	0.60	1.55
Thr	263	.	.	B	B	.	.	.	1.81	-0.47	*	.	F	0.60	1.58
Thr	264	.	.	B	B	.	.	.	1.77	-0.47	*	.	F	0.82	2.00
Thr	265	.	.	B	B	.	.	.	0.80	-0.90	*	.	F	1.34	4.67
Lys	266	.	.	B	B	.	.	.	1.01	-0.90	*	.	F	1.56	2.40
Arg	267	.	.	B	.	.	.	.	1.57	-0.99	*	.	F	1.98	2.68
Glu	268	.	.	B	.	.	.	.	1.29	-1.09	*	.	F	2.20	2.49
Val	269	.	.	B	.	.	.	.	0.74	-1.07	*	.	F	1.98	1.26
Asn	270	.	.	B	.	.	.	.	1.06	-0.43	*	*	F	1.31	0.48
Ser	271	.	.	B	.	.	.	.	0.20	-0.03	*	*	.	0.94	0.44
Ala	272	.	.	B	.	.	.	.	0.09	0.66	*	*	.	-0.18	0.49
Val	273	.	.	B	.	.	.	.	-0.72	0.41	.	*	.	-0.40	0.49
Asn	274	.	.	B	.	.	.	.	-0.16	0.70	.	*	.	-0.40	0.30
Leu	275	.	.	B	.	.	.	.	-0.46	1.23	.	*	.	-0.40	0.31
Asn	276	.	.	B	.	.	.	.	-0.44	1.11	.	.	.	-0.40	0.57
Leu	277	.	.	.	.	.	.	C	0.14	1.39	.	.	.	-0.20	0.37
Trp	278	.	.	.	.	.	.	C	0.79	0.99	.	*	.	-0.20	0.78
Ser	279	.	.	.	.	.	.	C	0.44	0.73	.	.	.	-0.20	0.75
Trp	280	.	.	.	.	.	.	C	0.87	0.76	.	.	.	-0.20	0.90
Glu	281	.	.	.	.	.	.	C	0.48	0.50	.	.	.	-0.05	1.09
Pro	282	.	.	.	.	T	.	.	0.90	0.01	.	.	.	0.45	1.04
Gly	283	.	.	.	.	T	.	.	0.80	0.06	.	.	.	0.45	1.27

Table 5

		I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV

Met	1	A	A	.	.	.	.	.	-1.47	0.70	.	.	.	-0.60	0.31
Ala	2	A	A	.	.	.	.	.	-1.38	0.96	.	.	.	-0.60	0.20
Leu	3	A	A	.	.	.	.	.	-1.80	0.91	.	.	.	-0.60	0.21
Met	4	A	A	.	.	.	.	.	-2.27	1.17	.	.	.	-0.60	0.17
Leu	5	A	A	.	.	.	.	.	-2.69	1.20	.	.	.	-0.60	0.13
Ser	6	A	A	.	.	.	.	.	-2.39	1.39	.	*	.	-0.60	0.13
Leu	7	A	A	.	.	.	.	.	-2.61	1.09	.	.	.	-0.60	0.17
Val	8	A	A	.	.	.	.	.	-2.61	1.16	*	.	.	-0.60	0.17
Leu	9	A	A	.	.	.	.	.	-1.97	1.16	*	.	.	-0.60	0.11
Ser	10	A	A	.	.	.	.	.	-1.97	0.77	*	.	.	-0.60	0.26
Leu	11	.	A	B	.	.	.	.	-2.01	0.77	*	.	.	-0.60	0.28
Leu	12	.	A	B	.	.	.	.	-1.50	0.56	*	.	.	-0.60	0.34
Lys	13	.	A	B	.	.	.	.	-0.99	0.26	*	.	F	-0.15	0.34
Leu	14	.	A	.	.	.	.	C	-0.18	0.30	.	.	F	0.05	0.41
Gly	15	.	.	.	.	T	T	.	-0.17	0.01	*	.	F	0.65	0.86
Ser	16	.	.	.	.	.	T	C	0.64	0.24	*	*	F	0.45	0.45
Gly	17	.	.	.	.	.	T	C	0.60	0.64	*	.	F	0.15	0.95
Gln	18	.	.	B	.	.	T	.	-0.14	0.60	*	.	F	-0.05	0.71
Trp	19	.	.	B	B	.	.	.	0.32	0.96	.	.	.	-0.60	0.46
Gln	20	.	.	B	B	.	.	.	0.46	1.00	.	*	.	-0.60	0.46
Val	21	.	.	B	B	.	.	.	0.76	1.00	.	*	.	-0.60	0.41
Phe	22	.	.	B	B	.	.	.	1.14	0.60	.	*	.	-0.30	0.65
Gly	23	.	.	.	.	.	T	C	0.93	-0.31	.	.	.	1.50	0.75
Pro	24	.	.	.	.	T	T	.	0.37	-0.29	.	.	F	2.30	1.57
Asp	25	.	.	.	.	.	T	C	0.37	-0.29	.	.	F	2.40	1.34
Lys	26	.	.	.	.	.	T	C	0.63	-0.67	*	.	F	3.00	2.35
Pro	27	.	.	.	B	.	.	C	0.52	-0.60	*	.	F	2.30	1.54
Val	28	.	.	B	B	.	.	.	0.01	-0.34	*	.	.	1.20	0.76
Gln	29	.	.	B	B	.	.	.	-0.12	0.30	*	.	.	0.30	0.28
Ala	30	.	.	B	B	.	.	.	-0.12	0.73	.	.	.	-0.30	0.18
Leu	31	.	.	B	B	.	.	.	-0.17	0.30	.	.	.	-0.30	0.42
Val	32	.	.	B	B	.	.	.	-0.54	-0.34	.	.	.	0.30	0.41
Gly	33	A	.	.	B	.	.	.	-0.28	-0.24	.	.	F	0.45	0.41
Glu	34	A	A	.	.	.	.	.	-0.98	-0.24	.	.	F	0.45	0.50
Asp	35	A	A	.	.	.	.	.	-0.69	-0.14	.	.	F	0.45	0.58
Ala	36	A	A	.	.	.	.	.	-0.54	-0.40	.	.	.	0.30	0.79
Ala	37	A	A	.	B	.	.	.	-0.39	-0.26	.	.	.	0.30	0.24
Phe	38	A	A	.	B	.	.	.	-0.86	0.53	.	.	.	-0.60	0.13
Ser	39	A	A	.	B	.	.	.	-1.16	1.21	.	.	.	-0.60	0.10
Cys	40	A	A	.	B	.	.	.	-1.37	1.10	.	.	.	-0.60	0.14
Phe	41	A	A	.	B	.	.	.	-0.73	1.03	.	.	.	-0.60	0.24
Leu	42	.	A	.	B	.	.	C	-0.46	0.24	.	.	.	-0.10	0.36
Ser	43	.	.	.	.	.	T	C	0.24	0.34	.	*	F	0.45	0.98
Pro	44	.	.	.	.	.	T	C	-0.04	0.17	.	*	F	0.60	1.82
Lys	45	.	.	.	.	.	T	C	0.62	-0.11	.	*	F	1.20	2.23
Thr	46	A	.	.	.	.	T	.	0.73	-0.80	.	*	F	1.30	2.88
Asn	47	A	A	.	.	.	.	.	0.94	-0.69	.	*	F	0.90	1.88
Ala	48	A	A	.	.	.	.	.	1.24	-0.50	.	*	.	0.30	0.93
Glu	49	A	A	.	.	.	.	.	0.60	-0.50	.	*	.	0.45	1.12
Ala	50	A	A	.	.	.	.	.	0.67	-0.34	.	*	.	0.30	0.52
Met	51	A	A	.	.	.	.	.	0.28	-0.74	*	*	.	0.60	1.00
Glu	52	A	A	.	.	.	.	.	-0.42	-0.46	*	.	.	0.30	0.50
Val	53	A	A	.	.	.	.	.	0.28	0.33	*	.	.	-0.30	0.43
Arg	54	A	A	.	.	.	.	.	-0.07	-0.17	*	.	.	0.30	0.85
Phe	55	A	A	.	.	.	.	.	0.52	-0.36	*	*	.	0.30	0.48
Phe	56	A	.	.	.	.	T	.	0.42	0.04	*	*	.	0.25	1.13
Arg	57	A	.	.	.	.	T	.	0.12	0.19	*	*	.	0.10	0.50
Gly	58	.	.	.	.	T	T	.	0.68	0.57	*	.	F	0.35	0.77
Gln	59	.	.	.	.	T	T	.	-0.29	0.17	*	*	F	0.80	1.20
Phe	60	.	.	.	B	.	.	C	-0.44	0.03	*	*	F	0.05	0.45
Ser	61	.	.	.	B	.	.	C	0.22	0.67	*	*	F	-0.25	0.34
Ser	62	.	.	B	B	.	.	.	-0.70	0.74	*	*	.	-0.60	0.27
Val	63	.	.	B	B	.	.	.	-0.60	1.03	*	.	.	-0.60	0.25
Val	64	.	.	B	B	.	.	.	-0.49	1.00	*	.	.	-0.60	0.30
His	65	.	.	B	B	.	.	.	0.21	0.61	*	.	.	-0.26	0.43
Leu	66	.	.	B	B	.	.	.	0.17	0.23	*	.	.	0.38	0.98
Tyr	67	.	.	B	.	.	T	.	0.51	0.01	*	.	.	1.27	1.30
Arg	68	.	.	.	.	T	T	.	1.37	-0.63	*	.	F	3.06	1.92
Asp	69	.	.	.	.	T	T	.	2.22	-1.13	*	.	F	3.40	3.88
Gly	70	.	.	.	.	T	T	.	2.04	-1.41	*	.	F	3.06	4.29
Lys	71	.	.	.	.	T	.	.	2.16	-1.74	*	.	F	2.52	3.39
Asp	72	.	.	.	.	.	.	C	1.80	-0.96	.	.	F	1.98	1.76

Gln	73	.	.	.	.	.	.	C	1.69	-0.34	.	.	F	1.34	1.76
Pro	74	.	.	B	.	.	.	.	1.09	-0.37	.	.	F	0.80	1.52
Phe	75	.	.	B	.	.	.	.	1.22	0.24	.	.	.	-0.10	0.90
Met	76	.	.	B	.	.	.	.	1.18	0.67	.	.	.	-0.40	0.80
Gln	77	.	.	B	.	.	.	.	0.93	0.67	.	.	.	-0.40	0.90
Met	78	.	.	B	.	.	.	.	0.93	1.00	*	.	.	-0.25	1.63
Pro	79	.	.	B	.	.	.	.	0.80	0.61	*	*	.	0.09	2.85
Gln	80	.	.	.	.	T	.	.	1.61	0.43	*	*	F	0.98	1.63
Tyr	81	.	.	.	.	T	T	.	1.90	0.03	.	*	F	1.82	3.23
Gln	82	A	.	.	.	.	T	.	1.94	-0.10	.	*	F	2.36	3.01
Gly	83	.	.	.	.	T	T	.	1.73	-0.53	.	*	F	3.40	3.48
Arg	84	.	.	B	.	.	T	.	1.09	-0.24	.	*	F	2.36	1.83
Thr	85	.	.	B	.	.	.	.	1.13	-0.36	.	*	F	1.90	0.78
Lys	86	.	.	B	.	.	.	.	1.38	-0.76	.	*	F	2.24	1.59
Leu	87	.	.	B	.	.	.	.	1.08	-1.19	.	*	F	2.13	1.35
Val	88	.	.	B	.	.	T	.	0.53	-0.80	.	*	F	2.22	1.26
Lys	89	.	.	B	.	.	T	.	-0.17	-0.60	.	.	F	2.30	0.44
Asp	90	.	.	B	.	.	T	.	0.14	-0.10	*	.	F	1.77	0.54
Ser	91	.	.	B	.	.	T	.	-0.24	-0.79	*	.	.	1.84	1.26
Ile	92	A	A	.	.	.	.	.	0.68	-1.00	*	*	.	1.06	0.62
Ala	93	A	A	.	.	.	.	.	0.64	-1.00	.	*	F	0.98	0.73
Glu	94	A	A	.	.	.	.	.	0.30	-0.31	.	*	F	0.45	0.38
Gly	95	A	A	.	.	.	.	.	-0.51	-0.31	*	*	F	0.45	0.73
Arg	96	A	A	.	.	.	.	.	-0.10	-0.31	*	*	F	0.45	0.60
Ile	97	A	A	.	.	.	.	.	-0.02	-0.81	.	*	F	0.75	0.67
Ser	98	A	A	.	.	.	.	.	0.57	-0.13	*	*	.	0.30	0.56
Leu	99	A	A	.	.	.	.	.	0.57	-0.56	*	*	.	0.60	0.50
Arg	100	A	A	.	.	.	.	.	0.02	-0.16	*	*	.	0.45	1.14
Leu	101	A	A	.	.	.	.	.	-0.40	-0.16	*	*	.	0.30	0.60
Glu	102	.	A	B	.	.	.	.	-0.37	-0.06	*	*	.	0.45	1.04
Asn	103	.	A	B	.	.	.	.	-0.88	-0.10	.	*	.	0.30	0.40
Ile	104	.	A	B	.	.	.	.	-0.07	0.59	.	*	.	-0.60	0.40
Thr	105	.	A	B	.	.	.	.	-0.77	-0.10	.	.	.	0.30	0.38
Val	106	.	A	B	.	.	.	.	-0.30	0.40	.	.	.	-0.60	0.24
Leu	107	.	A	B	.	.	.	.	-1.11	0.43	.	.	.	-0.60	0.34
Asp	108	.	A	B	.	.	.	.	-1.36	0.43	.	.	.	-0.60	0.19
Ala	109	.	A	B	.	.	.	.	-0.81	0.70	.	.	.	-0.60	0.41
Gly	110	.	.	.	.	T	.	.	-1.17	0.49	*	.	.	0.00	0.49
Leu	111	.	.	B	.	.	T	.	-0.20	0.37	*	.	.	0.10	0.16
Tyr	112	.	.	B	.	.	T	.	-0.28	0.37	*	*	.	0.10	0.30
Gly	113	.	.	B	.	.	T	.	-0.58	0.56	*	*	.	-0.20	0.22
Cys	114	.	.	B	.	.	T	.	-0.29	0.51	*	*	.	-0.20	0.35
Arg	115	.	.	B	B	.	.	.	0.06	0.21	*	*	.	-0.30	0.30
Ile	116	.	.	B	B	.	.	.	0.57	-0.14	*	*	F	0.45	0.52
Ser	117	.	.	B	B	.	.	.	0.57	-0.19	*	*	F	0.76	1.31
Ser	118	.	.	B	.	.	T	.	0.67	0.00	*	*	F	1.32	1.05
Gln	119	.	.	B	.	.	T	.	1.33	0.76	.	*	F	0.58	2.35
Ser	120	.	.	.	.	T	T	.	1.27	0.47	.	*	F	1.14	3.03
Tyr	121	.	.	.	.	T	T	.	1.57	0.09	.	.	F	1.60	4.52
Tyr	122	.	A	.	.	T	.	.	0.98	0.20	.	.	.	0.89	2.64
Gln	123	.	A	B	.	.	.	.	0.99	0.49	.	.	.	0.03	1.38
Lys	124	.	A	B	.	.	.	.	0.99	1.01	*	.	.	-0.28	0.93
Ala	125	.	A	B	.	.	.	.	0.48	0.26	*	.	.	0.01	1.02
Ile	126	.	A	B	.	.	.	.	0.72	0.19	.	*	.	-0.30	0.49
Trp	127	.	A	B	.	.	.	.	0.11	0.19	.	*	.	-0.30	0.42
Glu	128	A	A	.	.	.	.	.	-0.19	0.83	*	*	.	-0.60	0.31
Leu	129	A	A	.	.	.	.	.	-0.82	0.71	*	*	.	-0.60	0.59
Gln	130	.	A	B	.	.	.	.	-1.04	0.53	.	*	.	-0.60	0.57
Val	131	.	A	B	.	.	.	.	-0.50	0.30	.	*	.	-0.30	0.27
Ser	132	.	A	.	.	.	.	C	-0.51	0.73	.	*	.	-0.40	0.33
Ala	133	.	A	.	.	.	.	C	-1.37	0.43	.	*	.	-0.40	0.25
Leu	134	.	A	B	.	.	.	.	-0.77	0.67	.	*	.	-0.60	0.25
Gly	135	.	A	.	.	T	.	.	-1.58	0.46	.	.	.	-0.20	0.29
Ser	136	.	.	B	B	.	.	.	-1.61	0.76	.	.	.	-0.60	0.24
Val	137	.	.	B	B	.	.	.	-1.61	0.94	.	.	.	-0.60	0.20
Pro	138	.	.	B	B	.	.	.	-1.91	0.64	.	.	.	-0.60	0.27
Leu	139	.	.	B	B	.	.	.	-1.69	0.90	.	.	.	-0.60	0.14
Ile	140	.	.	B	B	.	.	.	-1.69	1.01	.	.	.	-0.60	0.19
Ser	141	.	.	B	B	.	.	.	-1.63	0.80	.	.	.	-0.60	0.12
Ile	142	.	.	B	B	.	.	.	-1.63	1.13	.	.	.	-0.60	0.24
Ala	143	.	.	B	B	.	.	.	-1.42	1.09	*	.	.	-0.60	0.25
Gly	144	.	.	B	B	.	.	.	-0.50	0.40	*	.	.	-0.34	0.31
Tyr	145	.	.	B	B	.	.	.	0.39	0.01	*	*	.	0.22	0.87

Val	146	.	.	B	B	.	.	.	-0.20	-0.67	*	.	.	1.53	1.44
Asp	147	.	.	B	.	.	T	.	0.69	-0.49	*	*	F	2.04	1.02
Arg	148	.	.	B	.	.	T	.	0.47	-0.51	*	.	F	2.60	1.13
Asp	149	.	.	B	.	.	T	.	0.00	-0.59	*	.	F	2.34	1.25
Ile	150	.	.	B	.	.	T	.	-0.42	-0.54	*	.	.	1.78	0.62
Gln	151	.	A	B	.	.	.	.	0.43	0.03	*	.	.	0.22	0.17
Leu	152	.	A	B	.	.	.	.	0.13	0.43	*	.	.	-0.34	0.18
Leu	153	.	A	B	.	.	.	.	-0.28	0.81	*	.	.	-0.60	0.34
Cys	154	.	A	B	.	.	.	.	-0.62	0.51	.	*	.	-0.60	0.26
Gln	155	.	A	.	.	T	.	.	-0.02	0.54	*	*	F	-0.05	0.31
Ser	156	.	.	.	.	T	T	.	-0.72	0.77	*	.	F	0.35	0.40
Ser	157	.	.	.	.	T	T	.	-0.12	0.87	*	.	F	0.35	0.64
Gly	158	.	.	.	.	T	T	.	0.80	0.73	*	.	F	0.35	0.57
Trp	159	.	.	.	.	T	T	.	1.26	0.33	*	.	F	0.65	0.84
Phe	160	.	.	.	.	.	T	C	0.94	0.37	*	.	F	0.45	0.97
Pro	161	.	.	.	.	.	T	C	0.66	0.47	*	*	F	0.30	1.41
Arg	162	.	.	.	.	.	T	C	1.00	0.54	*	*	F	0.30	1.36
Pro	163	.	.	.	.	T	T	.	1.06	-0.37	*	*	F	1.40	3.13
Thr	164	.	.	.	.	T	.	.	1.39	-0.24	*	*	F	1.20	2.13
Ala	165	.	.	.	.	T	.	.	1.74	-0.67	*	*	F	1.50	2.17
Lys	166	.	.	.	.	T	.	.	1.74	-0.24	.	*	F	1.20	1.39
Trp	167	.	.	.	.	T	.	.	1.63	-0.24	.	*	F	1.54	1.49
Lys	168	.	.	.	.	.	.	C	1.50	-0.33	.	*	F	1.68	2.55
Gly	169	.	.	.	.	.	.	C	1.81	-0.40	.	*	F	2.02	1.26
Pro	170	.	.	.	.	.	T	C	2.40	0.00	.	*	F	1.96	2.08
Gln	171	.	.	.	.	T	T	.	1.54	-0.91	.	*	F	3.40	1.74
Gly	172	.	.	.	.	.	T	C	1.53	-0.23	.	.	F	2.56	1.45
Gln	173	.	.	B	.	.	T	.	1.18	-0.27	.	.	F	2.02	1.26
Asp	174	.	.	B	.	.	.	.	1.52	-0.21	.	.	F	1.82	1.05
Leu	175	.	.	B	.	.	.	.	1.43	-0.61	*	*	F	2.12	1.77
Ser	176	.	.	B	.	.	T	.	1.54	-0.66	*	*	F	2.32	1.37
Thr	177	.	.	B	.	.	T	.	1.58	-1.06	*	*	F	2.66	1.60
Asp	178	.	.	.	.	T	T	.	1.58	-0.57	*	*	F	3.40	2.80
Ser	179	.	.	.	.	.	T	C	1.69	-0.86	*	*	F	2.86	3.37
Arg	180	.	.	.	.	T	T	.	2.50	-1.24	*	*	F	3.06	4.57
Thr	181	.	.	.	.	T	T	.	2.20	-1.73	*	.	F	3.06	4.57
Asn	182	.	.	.	.	T	T	.	2.48	-1.11	*	.	F	3.06	3.37
Arg	183	.	.	B	.	.	T	.	2.13	-1.00	*	.	F	2.66	2.34
Asp	184	.	.	.	.	T	T	.	1.62	-0.57	*	.	F	3.40	1.61
Met	185	.	.	B	.	.	T	.	0.81	-0.37	*	.	.	2.06	0.82
His	186	.	.	B	.	.	T	.	1.12	0.01	*	.	.	1.12	0.36
Gly	187	.	.	B	.	.	T	.	0.27	0.01	*	*	.	0.78	0.36
Leu	188	.	.	B	B	.	.	.	0.16	0.66	*	*	.	-0.26	0.27
Phe	189	A	.	.	B	.	.	.	-0.73	0.04	.	*	.	-0.30	0.35
Asp	190	A	.	.	B	.	.	.	-0.43	0.23	.	*	.	-0.30	0.25
Val	191	A	.	.	B	.	.	.	-1.21	0.19	.	*	.	-0.30	0.40
Glu	192	A	.	.	B	.	.	.	-1.18	0.19	.	*	.	-0.30	0.38
Ile	193	A	.	.	B	.	.	.	-1.22	-0.11	.	*	.	0.30	0.33
Ser	194	A	.	.	B	.	.	.	-0.52	0.53	.	*	.	-0.60	0.33
Leu	195	A	A	.	B	.	.	.	-0.52	0.29	.	*	.	-0.30	0.33
Thr	196	A	A	.	B	.	.	.	0.33	0.29	.	*	.	-0.30	0.81
Val	197	A	A	.	B	.	.	.	-0.26	0.00	.	*	.	0.55	0.98
Gln	198	A	A	.	B	.	.	.	0.29	0.11	.	*	F	0.50	1.20
Glu	199	A	A	.	B	.	.	.	0.29	-0.14	.	.	F	1.20	0.82
Asn	200	.	.	.	.	T	T	.	0.21	-0.24	.	.	F	2.40	1.48
Ala	201	.	.	.	.	T	T	.	0.22	-0.20	.	.	F	2.50	0.60
Gly	202	.	.	.	.	T	T	.	0.41	-0.21	.	.	F	2.25	0.46
Ser	203	.	.	.	.	T	T	.	0.11	0.36	.	.	F	1.40	0.15
Ile	204	A	.	.	.	.	.	.	-0.49	0.34	*	*	.	0.40	0.21
Ser	205	A	.	.	.	.	.	.	-0.38	0.46	*	*	.	-0.15	0.21
Cys	206	.	.	B	.	.	.	.	0.18	0.03	*	*	.	-0.10	0.30
Ser	207	.	A	B	.	.	.	.	-0.07	0.14	*	*	.	-0.30	0.58
Met	208	A	A	.	.	.	.	.	0.20	-0.04	*	*	.	0.30	0.44
Arg	209	A	A	.	.	.	.	.	0.28	0.07	*	*	.	-0.15	1.11
His	210	A	A	.	.	.	.	.	0.28	0.19	.	.	.	-0.30	0.69
Ala	211	A	A	.	.	.	.	.	1.06	0.19	.	.	.	-0.30	0.93
His	212	A	A	.	.	.	.	.	1.36	-0.43	*	.	.	0.30	0.93
Leu	213	A	A	.	.	.	.	.	1.10	-0.43	*	.	.	0.45	1.18
Ser	214	A	A	.	.	.	.	.	0.99	-0.29	*	.	.	0.30	0.87
Arg	215	A	A	.	.	.	.	.	0.72	-0.79	*	*	F	0.90	1.10
Glu	216	A	A	.	.	.	.	.	1.42	-0.90	*	*	F	0.90	1.79
Val	217	A	.	.	B	.	.	.	0.60	-1.59	*	*	F	0.90	2.62
Glu	218	A	.	.	B	.	.	.	1.41	-1.33	*	*	F	0.75	0.99

Ser	219	A	.	.	B	.	.	.	0.82	-0.93	*	*	F	0.75	0.99
Arg	220	.	.	B	B	.	.	.	0.37	-0.24	*	*	F	0.45	0.94
Val	221	.	.	B	B	.	.	.	0.37	-0.46	.	*	F	0.45	0.54
Gln	222	A	.	.	B	.	.	.	0.93	-0.46	.	*	.	0.64	0.67
Ile	223	A	.	.	.	.	T	.	1.04	0.07	*	*	.	0.78	0.36
Gly	224	A	.	.	.	.	T	.	1.46	0.07	*	*	F	1.27	0.95
Asp	225	.	.	.	.	T	T	.	1.39	-0.57	.	*	F	3.06	1.07
Trp	226	.	.	.	.	T	T	.	2.21	-0.97	.	.	F	3.40	3.06
Arg	227	.	.	B	.	.	.	.	1.87	-1.16	*	.	F	2.46	4.20
Arg	228	.	.	.	.	T	T	.	2.76	-1.16	*	.	F	2.72	2.49
Lys	229	.	.	.	.	T	T	.	2.51	-0.76	*	.	F	2.38	4.10
His	230	.	.	.	.	T	T	.	2.17	-1.17	*	.	F	2.38	2.12
Gly	231	.	.	.	.	.	T	C	2.50	-0.74	*	.	F	2.18	1.07
Gln	232	.	.	.	.	T	.	.	2.50	-0.74	*	.	F	2.52	1.07
Ala	233	.	.	.	.	.	.	C	2.43	-0.74	*	.	F	2.66	1.54
Gly	234	.	.	.	.	T	T	.	2.14	-1.24	*	.	F	3.40	3.11
Lys	235	.	.	B	.	.	T	.	1.88	-0.91	*	.	F	2.66	2.81
Arg	236	.	.	.	.	T	T	.	1.92	-0.93	*	.	F	2.77	3.73
Lys	237	.	.	.	.	T	T	.	1.62	-1.04	*	.	F	2.48	5.05
Tyr	238	.	.	B	.	.	T	.	2.18	-1.09	.	.	F	1.79	3.39
Ser	239	.	.	B	.	.	T	.	1.63	-0.59	.	.	F	1.50	2.35
Ser	240	.	.	B	.	.	T	.	1.34	0.10	.	.	F	0.50	0.82
Ser	241	.	.	B	.	.	T	.	1.23	0.86	.	.	F	0.15	0.82
His	242	.	.	B	.	.	.	.	0.89	0.10	*	.	.	0.20	1.03
Ile	243	.	.	B	.	.	.	.	0.43	0.10	*	.	.	0.15	1.03
Tyr	244	.	.	B	.	.	.	.	0.52	0.50	*	.	.	-0.35	0.66
Asp	245	.	.	B	.	.	.	.	0.52	0.54	*	.	.	-0.40	0.75
Ser	246	.	.	B	.	.	.	.	0.01	0.43	*	.	F	-0.10	1.44
Phe	247	.	.	B	.	.	T	.	-0.26	0.43	*	.	F	-0.05	0.76
Pro	248	.	.	.	.	.	T	C	-0.07	0.06	*	.	F	0.45	0.61
Ser	249	.	.	.	.	.	T	C	-0.42	0.84	.	.	F	0.15	0.39
Leu	250	.	.	.	.	.	T	C	-0.42	1.07	.	.	.	0.00	0.45
Ser	251	.	.	B	.	.	.	.	-0.82	0.29	.	.	.	-0.10	0.49
Phe	252	.	.	B	B	.	.	.	-0.37	0.64	.	.	.	-0.60	0.31
Met	253	.	.	B	B	.	.	.	-1.04	1.01	.	.	.	-0.60	0.60
Asp	254	.	.	B	B	.	.	.	-1.56	1.01	.	.	.	-0.60	0.31
Phe	255	.	.	B	B	.	.	.	-0.63	1.31	.	.	.	-0.60	0.30
Tyr	256	.	.	B	B	.	.	.	-0.54	0.53	.	.	.	-0.60	0.59
Ile	257	.	.	B	B	.	.	.	-0.70	0.34	.	.	.	-0.30	0.54
Leu	258	.	.	B	B	.	.	.	-0.44	0.99	*	.	.	-0.60	0.47
Arg	259	.	.	B	B	.	.	.	-0.66	0.63	*	.	.	-0.35	0.29
Pro	260	.	.	.	B	T	.	.	-0.62	0.30	.	*	F	0.75	0.65
Val	261	.	.	.	B	T	.	.	-0.27	0.19	*	*	F	1.00	0.42
Gly	262	.	.	.	.	.	T	C	0.03	-0.50	*	*	F	2.35	0.42
Pro	263	.	.	.	.	T	T	.	0.89	0.00	*	*	F	2.50	0.28
Cys	264	.	.	B	.	.	T	.	-0.03	-0.43	*	*	F	1.85	0.74
Arg	265	.	.	B	.	.	T	.	-0.68	-0.39	.	*	.	1.45	0.62
Ala	266	.	A	B	.	.	.	.	-0.42	-0.17	.	*	.	0.80	0.30
Lys	267	.	A	B	.	.	.	.	-0.42	0.01	.	*	.	-0.05	0.55
Leu	268	.	A	B	.	.	.	.	-0.52	-0.13	.	*	.	0.30	0.28
Val	269	.	A	B	.	.	.	.	-0.67	0.36	.	*	.	-0.30	0.40
Met	270	A	A	.	.	.	.	.	-0.73	0.54	.	*	.	-0.60	0.16
Gly	271	A	A	.	.	.	.	.	-0.96	0.54	*	*	.	-0.60	0.40
Thr	272	A	A	.	.	.	.	.	-1.00	0.54	.	*	.	-0.60	0.44
Leu	273	A	A	.	.	.	.	.	-1.08	0.30	.	*	.	-0.30	0.77
Lys	274	A	A	.	.	.	.	.	-1.03	0.37	.	*	.	-0.30	0.55
Leu	275	A	A	.	.	.	.	.	-0.78	0.63	.	*	.	-0.60	0.31
Gln	276	A	A	.	.	.	.	.	-0.43	0.57	.	*	.	-0.60	0.37
Ile	277	.	A	B	.	.	.	.	-0.98	-0.11	.	*	.	0.30	0.32
Leu	278	A	A	.	.	.	.	.	-0.20	0.53	.	*	.	-0.60	0.29
Gly	279	A	A	.	.	.	.	.	-0.94	0.34	.	*	.	-0.30	0.23
Glu	280	A	A	.	.	.	.	.	-0.99	0.73	.	*	.	-0.60	0.28
Val	281	A	A	.	.	.	.	.	-0.99	0.69	*	*	.	-0.60	0.26
His	282	A	A	.	.	.	.	.	-0.06	0.00	*	*	.	0.30	0.45
Phe	283	A	A	.	.	.	.	.	0.54	-0.43	.	.	.	0.30	0.52
Val	284	A	A	.	.	.	.	.	0.86	0.00	.	*	.	0.45	1.07
Glu	285	A	A	.	.	.	.	.	0.56	-0.14	.	.	F	0.60	1.07
Lys	286	A	.	.	.	.	T	.	0.60	-0.26	*	.	F	1.00	1.66
Pro	287	A	.	.	.	.	T	.	-0.18	-0.36	*	.	F	1.00	1.85
His	288	A	.	.	.	.	T	.	0.52	-0.31	*	.	F	0.85	0.88
Ser	289	A	.	.	.	.	T	.	0.49	0.09	*	.	.	0.10	0.76
Leu	290	A	.	.	B	.	.	.	0.19	0.77	.	*	.	-0.60	0.35
Leu	291	.	.	B	B	.	.	.	-0.20	0.73	.	*	.	-0.60	0.34

Gln 292	.	.	B	B	.	.	.	-0.33	0.66	.	.	.	-0.60	0.25
Ile 293	.	.	B	B	.	.	.	-0.60	0.70	.	.	F	-0.45	0.30
Ser 294	.	.	B	.	.	T	.	-0.61	0.40	.	.	F	0.25	0.49
Gly 295	.	.	.	.	T	T	.	-0.11	0.20	.	.	F	0.65	0.41
Gly 296	.	.	.	.	T	T	.	-0.11	0.29	.	*	F	0.65	0.84
Ser 297	.	.	.	.	.	T	C	-0.07	0.29	*	.	F	0.45	0.52
Thr 298	.	.	B	B	.	.	.	0.87	-0.10	*	.	F	0.90	1.04
Thr 299	.	.	B	B	.	.	.	0.82	-0.53	*	.	F	1.50	2.11
Leu 300	.	.	B	B	.	.	.	0.96	-0.53	*	.	F	1.80	1.56
Lys 301	.	.	.	B	T	.	.	1.30	-0.49	*	.	F	2.20	1.67
Lys 302	.	.	.	.	T	.	.	1.39	-0.57	*	.	F	3.00	1.86
Gly 303	.	.	.	.	.	T	C	1.41	-0.63	*	.	F	2.70	3.49
Pro 304	.	.	.	.	.	T	C	1.42	-0.40	*	.	F	2.10	1.83
Asn 305	.	.	.	.	.	T	C	1.53	-0.01	*	.	F	1.80	1.23
Pro 306	.	.	.	.	T	T	.	1.28	0.77	*	.	F	0.80	1.08
Trp 307	.	.	.	.	T	.	.	0.93	0.77	.	.	.	0.15	1.08
Ser 308	.	.	.	.	.	.	C	1.07	0.73	.	.	.	-0.20	0.90
Phe 309	.	.	B	.	.	.	.	0.61	0.76	.	.	F	-0.25	0.90
Pro 310	.	.	B	.	.	.	.	0.02	0.90	.	.	F	-0.25	0.46
Ser 311	.	.	.	.	.	T	C	-0.58	0.49	.	.	F	0.15	0.34
Pro 312	.	.	.	.	T	T	.	-0.99	0.79	.	.	F	0.35	0.33
Cys 313	.	.	.	.	T	T	.	-0.90	0.79	.	.	.	0.20	0.18
Ala 314	.	.	B	.	T	T	.	-0.51	0.79	.	.	.	0.20	0.21
Leu 315	.	.	B	.	.	.	.	-0.69	0.89	.	.	.	-0.40	0.20
Phe 316	.	.	B	.	.	.	.	-0.78	0.89	.	.	.	-0.40	0.47
Pro 317	.	.	B	.	.	.	.	-0.96	0.74	.	.	.	-0.40	0.60
Thr 318	.	.	B	.	.	.	.	-0.68	0.67	.	.	.	-0.40	0.93

Table 6

	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Met 1	A	A	.	.	.	.	.	-0.04	-0.17	.	.	.	0.45	1.00
Glu 2	A	A	.	.	.	.	.	-0.24	-0.10	.	.	.	0.30	0.79
Pro 3	A	A	.	.	.	.	.	-0.67	-0.03	.	.	.	0.30	0.63
Ala 4	A	A	.	.	.	.	.	-0.31	0.23	.	*	.	-0.30	0.52
Ala 5	A	A	.	.	.	.	.	-0.62	0.11	.	*	.	-0.30	0.41
Ala 6	A	A	.	.	.	.	.	-0.32	0.90	.	.	.	-0.60	0.23
Leu 7	A	A	.	.	.	.	.	-0.21	0.86	.	.	.	-0.60	0.30
His 8	A	A	.	.	.	.	.	-0.21	0.36	*	.	.	-0.30	0.59
Phe 9	A	A	.	.	.	.	.	-0.21	0.29	*	.	.	-0.30	0.90
Ser 10	A	A	.	.	.	.	.	0.08	0.29	*	.	.	-0.15	1.11
Arg 11	A	.	.	.	.	T	.	-0.14	-0.01	*	.	F	1.00	1.09
Pro 12	A	.	.	.	.	T	.	-0.14	0.17	*	.	F	0.40	1.04
Ala 13	A	.	.	.	.	T	.	-0.92	0.07	*	.	F	0.25	0.64
Ser 14	A	.	.	.	.	T	.	-1.03	0.37	*	.	.	0.10	0.27
Leu 15	A	.	.	B	.	.	.	-1.54	1.06	.	.	.	-0.60	0.14
Leu 16	A	.	.	B	.	.	.	-1.96	1.31	.	*	.	-0.60	0.12
Leu 17	A	.	.	B	.	.	.	-2.56	1.20	.	.	.	-0.60	0.12
Leu 18	A	.	.	B	.	.	.	-2.63	1.50	.	*	.	-0.60	0.12
Leu 19	A	.	.	B	.	.	.	-2.92	1.39	.	.	.	-0.60	0.08
Ser 20	A	.	.	B	.	.	.	-2.92	1.20	.	.	.	-0.60	0.09
Leu 21	A	.	.	B	.	.	.	-2.97	1.20	.	.	.	-0.60	0.09
Cys 22	A	.	.	B	.	.	.	-2.46	1.16	.	*	.	-0.60	0.08
Ala 23	A	.	.	B	.	.	.	-2.23	0.86	.	*	.	-0.60	0.08
Leu 24	A	.	.	B	.	.	.	-1.42	0.97	.	*	.	-0.60	0.10
Val 25	A	.	.	B	.	.	.	-1.82	0.69	.	*	.	-0.60	0.33
Ser 26	A	.	.	B	.	.	.	-1.32	0.90	.	*	.	-0.60	0.28
Ala 27	A	.	.	B	.	.	.	-1.51	0.89	.	*	.	-0.60	0.50
Gln 28	A	.	.	B	.	.	.	-1.78	0.84	.	*	.	-0.60	0.50
Phe 29	.	.	B	B	.	.	.	-1.31	0.84	.	*	.	-0.60	0.28
Thr 30	.	.	B	B	.	.	.	-0.67	0.89	.	*	.	-0.60	0.27
Val 31	.	.	B	B	.	.	.	-0.96	0.81	.	*	.	-0.60	0.24
Val 32	.	.	.	B	.	.	C	-0.37	0.91	.	*	.	-0.40	0.28
Gly 33	.	.	.	B	.	.	C	-0.58	0.53	.	*	F	-0.25	0.31
Pro 34	.	.	.	.	.	T	C	-0.77	0.47	.	.	F	0.15	0.65
Ala 35	.	.	.	.	.	T	C	-1.27	0.51	.	.	F	0.15	0.62
Asn 36	.	.	.	.	.	T	C	-1.00	0.56	.	.	F	0.15	0.51
Pro 37	A	.	.	.	.	T	.	-0.74	0.63	.	.	.	-0.20	0.34
Ile 38	A	A	.	.	.	.	.	-1.26	0.81	.	.	.	-0.60	0.33
Leu 39	.	A	B	.	.	.	.	-1.39	0.96	*	.	.	-0.60	0.15

Ala	40	A	A	.	.	.	.	.	-0.80	0.99	*	.	.	-0.60	0.10
Met	41	A	A	.	.	.	.	.	-0.80	0.56	.	.	.	-0.60	0.24
Val	42	A	A	.	.	.	.	.	-0.90	0.27	.	.	.	-0.30	0.47
Gly	43	A	.	.	.	.	T	.	-0.32	0.07	.	.	F	0.25	0.67
Glu	44	A	.	.	.	.	T	.	-0.32	0.06	.	*	F	0.25	0.98
Asn	45	A	.	.	.	.	T	.	0.38	0.13	.	*	F	0.40	1.09
Thr	46	A	.	.	.	.	T	.	0.31	-0.51	.	*	F	1.30	2.15
Thr	47	A	A	.	.	.	.	.	1.13	-0.37	.	*	F	0.45	0.66
Leu	48	A	A	.	.	.	.	.	0.67	0.13	.	*	.	-0.30	0.56
Arg	49	A	A	.	.	.	.	.	0.37	0.41	.	*	.	-0.60	0.32
Cys	50	A	A	.	.	.	.	.	0.16	0.31	.	*	.	0.00	0.30
His	51	.	A	.	.	T	.	.	0.47	0.26	*	*	.	0.70	0.56
Leu	52	.	A	.	.	.	.	C	0.82	-0.43	*	*	.	1.40	0.49
Ser	53	.	.	.	.	.	T	C	1.63	-0.43	*	*	F	2.40	1.85
Pro	54	.	.	.	.	.	T	C	0.93	-0.60	*	*	F	3.00	2.18
Glu	55	A	.	.	.	.	T	.	1.60	-0.60	.	.	F	2.50	2.67
Lys	56	A	.	.	.	.	T	.	1.63	-1.29	.	.	F	2.20	3.45
Asn	57	A	A	.	.	.	.	.	1.84	-1.67	.	.	F	1.50	3.73
Ala	58	A	A	.	.	.	.	.	2.14	-1.49	.	.	F	1.20	2.13
Glu	59	A	A	.	.	.	.	.	1.50	-1.49	*	*	F	0.90	1.85
Asp	60	A	A	.	.	.	.	.	1.61	-0.84	*	*	F	0.75	0.85
Met	61	A	A	.	.	.	.	.	1.28	-1.24	*	*	.	0.75	1.65
Glu	62	A	A	.	.	.	.	.	0.58	-0.83	*	.	.	0.75	1.00
Val	63	A	A	.	.	.	.	.	1.28	-0.04	*	*	.	0.30	0.52
Arg	64	A	A	.	.	.	.	.	0.98	-0.04	*	*	.	0.45	1.03
Trp	65	A	A	.	.	.	.	.	0.98	-0.27	*	*	.	0.30	0.80
Phe	66	A	A	.	.	.	.	.	0.88	0.13	*	*	.	-0.15	1.86
Arg	67	.	A	.	.	T	.	.	0.58	0.27	*	*	F	0.25	0.82
Ser	68	.	.	.	.	T	T	.	1.22	0.66	*	*	F	0.50	1.05
Gln	69	.	.	.	.	T	T	.	0.52	0.17	*	*	F	0.80	1.87
Phe	70	.	.	.	.	.	T	C	-0.04	-0.11	.	*	F	1.05	0.96
Ser	71	.	.	.	.	.	T	C	-0.04	0.53	.	*	F	0.15	0.53
Pro	72	.	.	.	B	.	.	C	-1.01	0.93	.	*	.	-0.40	0.27
Ala	73	.	.	.	B	T	.	.	-0.96	1.17	.	.	.	-0.20	0.23
Val	74	.	.	B	B	.	.	.	-0.91	1.14	.	*	.	-0.44	0.27
Phe	75	.	.	B	B	.	.	.	-0.56	0.76	.	.	.	-0.28	0.35
Val	76	.	.	B	B	.	.	.	-0.60	0.76	*	.	.	-0.12	0.34
Tyr	77	.	.	.	.	T	T	.	-0.28	0.69	*	.	.	0.84	0.45
Lys	78	.	.	.	.	T	T	.	0.31	0.04	.	*	F	1.60	1.02
Gly	79	.	.	.	.	.	T	C	1.28	-0.74	.	*	F	2.14	2.39
Gly	80	.	.	.	.	.	T	C	1.67	-1.39	*	*	F	1.98	2.98
Arg	81	.	A	.	.	.	.	C	2.52	-1.66	*	*	F	1.42	2.15
Glu	82	.	A	.	.	.	.	C	2.77	-1.66	.	*	F	1.26	3.77
Arg	83	A	A	.	.	.	.	.	2.72	-2.09	.	*	F	0.90	6.59
Thr	84	A	A	.	.	.	.	.	2.47	-2.11	.	*	F	0.90	5.83
Glu	85	A	A	.	.	.	.	.	2.81	-1.50	.	*	F	0.90	3.33
Glu	86	A	A	.	.	.	.	.	2.70	-1.50	.	*	F	0.90	2.95
Gln	87	A	A	.	.	.	.	.	2.46	-1.50	.	*	F	0.90	3.53
Met	88	A	A	.	.	.	.	.	2.46	-1.23	.	*	F	0.90	3.20
Glu	89	A	A	.	.	.	.	.	2.42	-1.23	.	*	F	0.90	3.62
Glu	90	A	A	.	.	.	.	.	2.53	-0.80	.	*	F	0.90	2.07
Tyr	91	A	.	.	.	.	T	.	1.64	-1.20	.	*	F	1.30	4.09
Arg	92	A	.	.	.	.	T	.	1.33	-1.13	.	*	F	1.30	1.66
Gly	93	A	.	.	.	.	T	.	1.23	-0.64	.	*	F	1.30	1.38
Arg	94	A	.	.	.	.	T	.	0.38	0.14	.	*	F	0.25	0.76
Ile	95	A	.	.	B	.	.	.	0.08	0.03	.	*	.	-0.30	0.29
Thr	96	A	.	.	B	.	.	.	0.37	0.41	.	*	.	-0.60	0.39
Phe	97	.	.	B	B	.	.	.	0.26	-0.01	*	*	.	0.64	0.40
Val	98	.	.	B	B	.	.	.	-0.29	-0.01	*	*	.	0.98	0.95
Ser	99	.	.	B	.	.	T	.	-0.40	-0.01	*	*	F	1.87	0.46
Lys	100	.	.	.	.	T	T	.	0.60	-0.10	*	.	F	2.61	0.86
Asp	101	.	.	.	.	T	T	.	0.57	-0.89	*	.	F	3.40	2.27
Ile	102	.	.	.	.	.	T	C	0.97	-1.10	*	.	F	2.86	1.67
Asn	103	.	.	.	.	T	T	.	0.97	-1.10	*	.	F	2.72	1.12
Arg	104	.	.	.	.	T	T	.	0.68	-0.46	*	*	F	1.93	0.50
Gly	105	.	.	.	.	T	T	.	-0.18	0.04	*	.	F	0.99	0.72
Ser	106	A	.	.	.	.	T	.	-1.03	0.04	*	*	F	0.25	0.37
Val	107	A	.	.	B	.	.	.	-1.03	0.29	.	*	.	-0.30	0.14
Ala	108	A	.	.	B	.	.	.	-1.07	0.97	.	*	.	-0.60	0.10
Leu	109	.	.	B	B	.	.	.	-1.18	1.04	.	*	.	-0.60	0.10
Val	110	.	.	B	B	.	.	.	-1.69	1.06	*	.	.	-0.60	0.22
Ile	111	.	.	B	B	.	.	.	-1.70	1.06	.	.	.	-0.60	0.16
His	112	A	.	.	B	.	.	.	-1.43	1.04	.	.	.	-0.60	0.28

Asn	113	A	.	.	B	.	.	.	-0.84	0.86	.	.	.	-0.60	0.38
Val	114	A	.	.	B	.	.	.	-0.03	0.61	.	.	.	-0.60	0.94
Thr	115	A	.	.	B	.	.	.	0.82	-0.07	.	*	.	0.45	1.20
Ala	116	A	.	.	B	.	.	.	1.37	-0.17	.	.	F	0.88	1.20
Gln	117	A	.	.	.	.	T	.	0.51	-0.14	.	.	F	1.56	1.60
Glu	118	.	.	.	.	T	T	.	0.27	-0.10	*	*	F	2.09	0.77
Asn	119	.	.	.	.	T	T	.	1.23	0.17	*	*	F	1.92	1.20
Gly	120	.	.	.	.	T	T	.	0.88	-0.33	*	*	F	2.80	1.36
Ile	121	.	.	.	.	T	.	.	1.22	-0.16	.	*	.	2.02	0.42
Tyr	122	.	.	.	.	T	.	.	0.52	0.60	*	*	.	0.84	0.41
Arg	123	.	.	.	.	T	.	.	0.52	0.99	*	*	.	0.56	0.36
Cys	124	.	.	B	.	.	.	.	0.52	0.96	*	*	.	-0.12	0.89
Tyr	125	.	.	B	.	.	.	.	0.52	0.27	*	*	.	-0.10	0.98
Phe	126	.	.	B	.	.	.	.	1.52	-0.06	*	.	.	0.84	0.49
Gln	127	.	.	.	.	T	.	.	1.47	-0.06	*	*	F	1.88	1.81
Glu	128	.	.	.	.	T	.	.	1.11	-0.24	*	.	F	2.22	1.55
Gly	129	.	.	.	.	T	T	.	1.78	-0.24	*	.	F	2.76	2.80
Arg	130	.	.	.	.	T	T	.	2.02	-1.03	*	.	F	3.40	2.70
Ser	131	.	.	.	.	.	T	C	2.13	-1.43	*	.	F	2.86	2.70
Tyr	132	A	.	.	.	.	T	.	1.24	-0.93	*	.	F	2.32	2.75
Asp	133	A	A	.	.	.	.	.	0.43	-0.67	*	*	F	1.43	0.99
Glu	134	A	A	.	.	.	.	.	0.89	0.01	*	*	.	0.04	0.61
Ala	135	A	A	.	.	.	.	.	-0.03	-0.37	*	*	.	0.30	0.76
Ile	136	A	A	.	.	.	.	.	-0.59	-0.44	*	*	.	0.30	0.37
Leu	137	A	A	.	.	.	.	.	-1.20	0.20	*	*	.	-0.30	0.16
Arg	138	A	A	.	.	.	.	.	-1.79	0.84	*	*	.	-0.60	0.12
Leu	139	A	A	.	.	.	.	.	-2.13	0.84	*	*	.	-0.60	0.17
Val	140	A	A	.	.	.	.	.	-2.36	0.59	*	*	.	-0.60	0.20
Val	141	A	A	.	.	.	.	.	-1.81	0.59	*	*	.	-0.60	0.09
Ala	142	A	A	.	.	.	.	.	-1.30	1.01	.	*	.	-0.60	0.10
Gly	143	.	A	.	.	T	.	.	-1.37	0.71	.	*	.	-0.20	0.19
Leu	144	.	.	.	.	.	.	C	-0.77	0.07	.	.	.	0.10	0.50
Gly	145	.	.	.	.	.	.	C	-0.72	-0.14	.	.	F	0.85	0.77
Ser	146	.	.	.	.	.	.	C	-0.76	0.04	*	.	F	0.25	0.64
Lys	147	.	A	.	.	.	.	C	-0.17	0.30	*	*	F	0.05	0.54
Pro	148	A	A	.	.	.	.	.	-0.71	-0.39	.	*	F	0.45	0.95
Leu	149	A	A	.	.	.	.	.	0.14	-0.13	.	*	.	0.30	0.50
Ile	150	A	A	.	.	.	.	.	-0.10	-0.51	*	*	.	0.60	0.50
Glu	151	A	A	.	.	.	.	.	0.20	-0.01	.	*	.	0.30	0.33
Ile	152	A	A	.	.	.	.	.	0.16	-0.04	.	*	.	0.30	0.68
Lys	153	A	A	.	.	.	.	.	0.37	-0.73	.	*	F	1.24	1.69
Ala	154	A	A	.	.	.	.	.	0.83	-1.41	.	*	F	1.58	1.63
Gln	155	A	A	.	.	.	.	.	1.42	-0.99	.	*	F	1.92	2.30
Glu	156	A	.	.	.	.	T	.	0.53	-1.29	.	*	F	2.66	1.54
Asp	157	.	.	.	.	T	T	.	1.13	-0.60	.	*	F	3.40	1.07
Gly	158	.	.	.	.	T	T	.	0.28	-0.19	*	*	F	2.61	0.65
Ser	159	.	.	.	.	T	T	.	0.87	0.10	.	*	F	1.67	0.31
Ile	160	A	A	.	.	.	.	.	0.20	0.10	*	*	.	0.38	0.32
Trp	161	A	A	.	.	.	.	.	-0.69	0.67	*	.	.	-0.26	0.17
Leu	162	A	A	.	.	.	.	.	-0.99	0.93	.	*	.	-0.60	0.09
Glu	163	.	A	B	.	.	.	.	-0.99	0.93	*	.	.	-0.60	0.17
Cys	164	.	A	.	.	T	.	.	-1.03	0.67	*	.	.	-0.20	0.16
Ile	165	.	.	.	.	T	.	.	-0.43	0.19	.	.	.	0.30	0.20
Ser	166	.	.	.	.	T	T	.	-0.39	0.41	*	.	.	0.20	0.12
Gly	167	.	.	.	.	T	T	.	0.21	1.17	.	.	F	0.35	0.35
Gly	168	.	.	.	.	T	T	.	0.21	1.03	.	.	F	0.35	0.77
Trp	169	.	.	.	.	.	T	C	0.67	0.34	.	.	F	0.45	0.99
Tyr	170	.	.	.	.	.	T	C	0.74	0.39	.	.	F	0.60	1.55
Pro	171	.	.	.	.	.	T	C	0.73	0.64	.	.	F	0.30	1.29
Glu	172	.	.	.	.	.	T	C	0.22	0.70	.	.	F	0.30	1.77
Pro	173	.	.	.	.	T	T	.	0.28	0.43	*	.	F	0.35	0.84
Leu	174	.	.	.	B	T	.	.	0.68	0.59	*	.	.	-0.20	0.57
Thr	175	.	.	.	B	T	.	.	0.92	0.16	*	.	.	0.10	0.64
Val	176	.	.	.	B	T	.	.	0.92	0.16	*	.	.	0.10	0.70
Trp	177	.	.	.	B	T	.	.	0.68	0.16	*	.	.	0.59	1.31
Arg	178	.	.	.	B	.	.	C	0.54	0.23	*	.	.	0.73	1.42
Asp	179	.	.	.	.	.	T	C	1.36	0.17	*	.	F	1.62	1.89
Pro	180	.	.	.	.	T	T	.	0.81	-0.47	*	.	F	2.76	3.11
Tyr	181	.	.	.	.	T	T	.	0.81	-0.74	*	.	F	3.40	1.18
Gly	182	.	.	.	.	T	T	.	0.89	-0.10	*	.	F	2.61	0.52
Glu	183	.	.	.	B	T	.	.	0.19	0.33	*	.	.	1.12	0.52
Val	184	A	.	.	B	.	.	.	-0.62	0.40	*	*	.	0.08	0.34
Val	185	A	.	.	B	.	.	.	-0.37	0.33	*	.	.	0.04	0.28

Pro	186	A	A	.	.	.	.	.	-0.12	-0.10	*	.	.	0.30	0.33
Ala	187	A	A	.	.	.	.	.	-0.63	-0.10	*	.	.	0.30	0.76
Leu	188	A	A	.	.	.	.	.	-0.93	-0.10	*	.	.	0.30	0.76
Lys	189	A	A	.	.	.	.	.	-0.97	-0.36	*	.	F	0.45	0.66
Glu	190	A	A	.	.	.	.	.	-0.70	-0.10	.	.	.	0.30	0.46
Val	191	A	A	.	.	.	.	.	-0.49	-0.10	.	.	.	0.30	0.56
Ser	192	A	A	.	.	.	.	.	-0.49	-0.79	.	.	.	0.60	0.47
Ile	193	A	A	.	.	.	.	.	0.32	-0.29	.	.	.	0.30	0.27
Ala	194	A	A	.	.	.	.	.	-0.07	-0.29	.	.	.	0.30	0.61
Asp	195	A	.	.	.	.	T	.	-0.88	-0.50	.	.	.	0.70	0.45
Ala	196	A	.	.	.	.	T	.	-0.72	-0.20	.	.	F	0.85	0.53
Asp	197	A	.	.	.	.	T	.	-1.02	-0.10	.	.	F	0.85	0.46
Gly	198	A	.	.	.	.	T	.	-0.99	0.01	.	*	.	0.10	0.27
Leu	199	A	.	.	B	.	.	.	-0.71	0.66	.	*	.	-0.60	0.20
Phe	200	A	.	.	B	.	.	.	-1.02	0.64	.	*	.	-0.60	0.17
Met	201	A	.	.	B	.	.	.	-1.02	1.13	*	.	.	-0.60	0.25
Val	202	A	.	.	B	.	.	.	-1.88	1.20	.	.	.	-0.60	0.31
Thr	203	A	.	.	B	.	.	.	-2.42	1.16	.	.	.	-0.60	0.26
Thr	204	A	.	.	B	.	.	.	-2.50	1.06	*	*	.	-0.60	0.19
Ala	205	A	.	.	B	.	.	.	-1.69	1.13	*	*	.	-0.60	0.18
Val	206	A	.	.	B	.	.	.	-1.09	0.49	.	*	.	-0.60	0.24
Ile	207	A	.	.	B	.	.	.	-0.19	0.00	.	*	.	-0.30	0.28
Ile	208	A	.	.	B	.	.	.	-0.12	-0.49	.	*	.	0.53	0.55
Arg	209	A	.	.	B	.	.	.	-0.67	-0.23	.	.	.	0.91	1.15
Asp	210	.	.	.	B	T	.	.	0.03	-0.23	.	.	.	1.54	1.22
Lys	211	.	.	.	B	T	.	.	0.89	-0.91	.	.	F	2.22	3.42
Tyr	212	.	.	.	B	T	.	.	0.92	-1.20	*	.	.	2.30	2.80
Val	213	.	.	.	B	T	.	.	1.51	-0.56	*	*	.	2.07	1.25
Arg	214	.	.	.	B	T	.	.	0.73	-0.17	*	.	.	1.39	0.84
Asn	215	.	.	.	.	T	T	.	0.43	0.40	*	.	.	0.66	0.29
Val	216	.	.	B	.	.	T	.	-0.47	0.03	*	.	.	0.33	0.52
Ser	217	.	.	.	.	T	T	.	-0.22	0.03	*	.	.	0.50	0.20
Cys	218	.	.	.	.	T	T	.	0.63	0.43	*	.	.	0.20	0.20
Ser	219	.	.	.	.	T	T	.	0.21	0.43	*	*	.	0.20	0.42
Val	220	.	.	.	.	T	T	.	-0.60	0.27	*	*	.	0.50	0.46
Asn	221	.	.	.	.	T	T	.	-0.56	0.57	.	*	F	0.35	0.70
Asn	222	.	.	.	.	.	T	C	-0.60	0.69	.	.	F	0.15	0.43
Thr	223	.	A	.	B	.	.	C	0.07	0.73	.	.	F	-0.25	0.58
Leu	224	.	A	.	B	.	.	C	0.37	0.49	.	.	F	-0.25	0.62
Leu	225	A	A	.	B	.	.	.	1.27	0.09	.	.	F	-0.15	0.67
Gly	226	A	A	.	B	.	.	.	1.27	-0.31	.	.	F	0.45	0.93
Gln	227	A	A	.	.	.	.	.	0.96	-0.80	.	.	F	0.90	1.94
Glu	228	A	A	.	.	.	.	.	0.41	-1.00	.	.	F	0.90	3.40
Lys	229	A	A	.	B	.	.	.	0.33	-1.04	.	.	F	0.90	2.55
Glu	230	A	A	.	B	.	.	.	0.44	-0.79	.	.	F	0.90	1.03
Thr	231	A	A	.	B	.	.	.	-0.10	-0.40	.	.	F	0.45	0.52
Val	232	A	A	.	B	.	.	.	-0.31	0.29	.	.	.	-0.30	0.18
Ile	233	A	A	.	B	.	.	.	-0.31	0.71	.	.	.	-0.60	0.16
Phe	234	A	.	.	B	.	.	.	-0.66	0.71	*	.	.	-0.60	0.19
Ile	235	A	.	.	.	.	T	.	-1.36	0.61	*	.	.	-0.20	0.35
Pro	236	A	.	.	.	.	T	.	-1.64	0.76	.	.	F	-0.05	0.43
Glu	237	.	.	.	.	T	T	.	-1.00	0.69	.	.	F	0.35	0.49
Ser	238	.	.	.	.	T	T	.	-0.41	0.33	.	.	F	0.80	1.09
Phe	239	.	.	.	.	.	.	C	-0.30	0.03	.	.	.	0.10	0.94
Met	240	.	.	.	.	.	T	C	0.29	0.10	*	.	.	0.30	0.55
Pro	241	.	.	.	.	.	T	C	0.29	0.49	*	.	F	0.15	0.55
Ser	242	.	.	.	.	T	T	.	0.00	0.53	*	.	F	0.35	0.98
Ala	243	.	.	.	.	.	T	C	-0.30	0.66	.	.	F	0.30	1.05
Ser	244	.	.	.	.	.	T	C	-0.46	0.66	.	.	F	0.15	0.67
Pro	245	A	.	.	.	.	T	.	-0.44	0.87	.	.	.	-0.20	0.37
Trp	246	A	.	.	.	.	T	.	-1.04	0.99	.	.	.	-0.20	0.37
Met	247	A	.	.	.	.	T	.	-1.33	1.17	.	.	.	-0.20	0.23
Val	248	A	.	.	B	.	.	.	-1.60	1.29	.	.	.	-0.60	0.15
Ala	249	A	.	.	B	.	.	.	-2.19	1.50	.	.	.	-0.60	0.11
Leu	250	A	.	.	B	.	.	.	-2.79	1.27	.	.	.	-0.60	0.07
Ala	251	A	.	.	B	.	.	.	-2.81	1.34	.	.	.	-0.60	0.08
Val	252	A	.	.	B	.	.	.	-2.80	1.19	.	.	.	-0.60	0.12
Ile	253	A	.	.	B	.	.	.	-2.24	1.19	.	.	.	-0.60	0.14
Leu	254	A	.	.	B	.	.	.	-1.87	0.89	.	.	.	-0.60	0.19
Thr	255	A	.	.	B	.	.	.	-1.34	0.81	.	.	.	-0.60	0.40
Ala	256	A	.	.	B	.	.	.	-1.36	1.09	.	.	.	-0.60	0.60
Ser	257	.	.	.	.	.	T	C	-1.36	1.01	.	.	F	0.15	0.72
Pro	258	.	.	.	.	T	T	.	-0.77	0.97	.	.	.	0.20	0.37

Trp	259	.	.	.	.	T	T	.	-0.56	0.87	.	.	.	0.20	0.49
Met	260	A	.	.	.	.	T	.	-0.56	0.99	.	.	.	-0.20	0.36
Val	261	A	.	.	B	.	.	.	-0.82	1.09	.	.	.	-0.60	0.34
Ser	262	A	.	.	B	.	.	.	-1.41	1.30	.	.	.	-0.60	0.24
Met	263	A	.	.	B	.	.	.	-2.01	1.07	.	.	.	-0.60	0.17
Thr	264	A	.	.	B	.	.	.	-2.31	1.14	.	*	.	-0.60	0.19
Val	265	A	.	.	B	.	.	.	-2.57	1.00	.	.	.	-0.60	0.14
Ile	266	A	.	.	B	.	.	.	-2.41	1.26	.	.	.	-0.60	0.11
Leu	267	A	.	.	B	.	.	.	-3.00	1.43	.	.	.	-0.60	0.06
Ala	268	A	.	.	B	.	.	.	-3.29	1.63	.	.	.	-0.60	0.06
Val	269	A	.	.	B	.	.	.	-3.68	1.67	.	.	.	-0.60	0.06
Phe	270	A	.	.	B	.	.	.	-3.42	1.77	.	.	.	-0.60	0.06
Ile	271	A	.	.	B	.	.	.	-3.12	1.70	.	.	.	-0.60	0.06
Ile	272	A	.	.	B	.	.	.	-3.17	1.70	.	.	.	-0.60	0.08
Phe	273	A	.	.	B	.	.	.	-2.88	1.70	.	.	.	-0.60	0.07
Met	274	A	.	.	B	.	.	.	-2.91	1.30	.	.	.	-0.60	0.14
Ala	275	A	.	.	B	.	.	.	-2.88	1.30	.	.	.	-0.60	0.14
Val	276	A	.	.	B	.	.	.	-2.66	1.19	.	.	.	-0.60	0.09
Ser	277	A	.	.	B	.	.	.	-2.66	0.97	.	.	.	-0.60	0.05
Ile	278	A	.	.	B	.	.	.	-1.91	1.04	*	.	.	-0.60	0.03
Cys	279	A	.	.	B	.	.	.	-1.27	0.54	*	.	.	-0.60	0.09
Cys	280	A	.	.	B	.	.	.	-1.49	-0.10	.	.	.	0.30	0.13
Ile	281	A	.	.	B	.	.	.	-0.63	0.20	*	.	.	-0.30	0.15
Lys	282	A	.	.	B	.	.	.	-0.22	-0.09	*	.	.	0.30	0.49
Lys	283	A	A	.	.	.	.	.	0.67	-0.66	*	.	F	0.90	1.80
Leu	284	A	A	.	.	.	.	.	1.38	-1.23	*	.	F	0.90	4.44
Gln	285	A	A	.	.	.	.	.	2.09	-1.91	*	.	F	0.90	4.44
Arg	286	A	A	.	.	.	.	.	2.09	-1.91	*	.	F	0.90	4.44
Glu	287	A	A	.	.	.	.	.	1.23	-1.23	*	.	F	0.90	3.78
Lys	288	A	A	.	.	.	.	.	0.89	-1.23	*	.	F	0.90	1.80
Lys	289	A	A	.	.	.	.	.	1.36	-1.24	*	.	F	0.90	1.23
Ile	290	A	A	.	.	.	.	.	1.36	-0.81	*	.	F	0.75	0.70
Leu	291	A	.	.	.	.	T	.	1.29	-0.81	*	.	F	1.15	0.61
Ser	292	A	.	.	.	.	T	.	1.33	-0.81	*	.	F	1.15	0.61
Gly	293	A	.	.	.	.	T	.	0.43	-0.81	*	*	F	1.30	1.74
Glu	294	A	.	.	.	.	T	.	0.39	-0.86	*	.	F	1.30	1.56
Lys	295	A	A	.	.	.	.	.	1.28	-1.54	*	*	F	0.90	2.02
Lys	296	A	A	.	.	.	.	.	2.09	-1.53	.	*	F	0.90	3.53
Val	297	A	A	.	.	.	.	.	2.39	-1.96	*	*	F	0.90	3.53
Glu	298	A	A	.	.	.	.	.	2.78	-1.96	*	*	F	0.90	3.06
Gln	299	A	A	.	.	.	.	.	2.78	-1.96	*	.	F	0.90	3.06
Glu	300	A	A	.	.	.	.	.	1.84	-1.96	*	.	F	0.90	7.14
Glu	301	A	A	.	.	.	.	.	1.21	-1.91	*	*	F	0.90	2.89
Lys	302	A	A	.	.	.	.	.	2.07	-1.41	*	.	F	0.90	1.69
Glu	303	A	A	.	.	.	.	.	2.07	-1.41	*	.	F	0.90	1.69
Ile	304	A	A	.	.	.	.	.	1.26	-1.01	*	.	.	0.75	1.69
Ala	305	A	A	.	.	.	.	.	1.26	-0.33	*	.	.	0.30	0.70
Gln	306	A	A	.	.	.	.	.	1.26	0.07	*	.	.	-0.30	0.70
Gln	307	A	A	.	.	.	.	.	1.21	0.07	*	*	F	0.00	1.72
Leu	308	A	A	.	.	.	.	.	0.40	-0.61	*	*	F	0.90	2.95
Gln	309	A	A	.	.	.	.	.	1.40	-0.43	*	*	F	0.60	1.40
Glu	310	A	A	.	.	.	.	.	1.70	-0.83	*	*	F	0.90	1.59
Glu	311	A	A	.	.	.	.	.	1.81	-0.31	*	*	F	0.60	2.02
Leu	312	A	A	.	.	.	.	.	1.92	-1.00	.	*	.	0.75	2.29
Arg	313	A	A	.	.	.	.	.	2.42	-1.40	*	*	.	0.75	2.59
Trp	314	A	A	.	.	.	.	.	1.72	-0.91	*	*	.	0.75	2.16
Arg	315	A	A	.	.	.	.	.	0.91	-0.13	*	*	.	0.45	2.26
Arg	316	A	A	.	.	.	.	.	0.88	-0.13	*	*	.	0.30	0.95
Thr	317	A	A	.	.	.	.	.	1.10	0.37	*	*	.	-0.15	1.23
Phe	318	A	A	.	.	.	.	.	0.40	-0.04	*	*	.	0.30	0.64
Leu	319	A	A	.	.	.	.	.	0.69	0.46	*	.	.	-0.60	0.33
His	320	.	A	.	.	.	.	C	-0.28	0.46	*	.	.	-0.40	0.38
Ala	321	A	A	.	.	.	.	.	-1.24	0.61	*	*	.	-0.60	0.33
Ala	322	A	A	.	.	.	.	.	-1.74	0.47	*	.	.	-0.60	0.29
Asp	323	A	A	.	.	.	.	.	-1.04	0.47	*	.	.	-0.60	0.18
Val	324	A	A	.	.	.	.	.	-0.44	-0.03	.	*	.	0.30	0.29
Val	325	A	A	.	.	.	.	.	-0.41	-0.10	*	*	.	0.58	0.45
Leu	326	A	A	.	.	.	.	.	-0.13	-0.60	.	*	.	1.16	0.45
Asp	327	A	.	.	.	.	T	.	-0.13	-0.11	.	*	F	1.69	0.87
Pro	328	A	.	.	.	.	T	.	-0.17	-0.26	.	*	F	2.12	1.19
Asp	329	.	.	.	.	T	T	.	0.48	-0.40	.	.	F	2.80	1.96
Thr	330	A	.	.	.	.	T	.	1.33	-0.66	.	.	F	2.42	1.82
Ala	331	A	A	.	.	.	.	.	1.33	-0.66	.	.	F	1.74	2.03

His	332	A	A	.	.	.	.	.	0.63	-0.40	.	.	F	1.16	1.00
Pro	333	A	A	.	.	.	.	.	0.03	0.39	.	.	F	0.13	0.60
Glu	334	A	A	.	.	.	.	.	-0.27	0.59	.	.	.	-0.60	0.49
Leu	335	A	A	.	.	.	.	.	0.04	0.47	.	*	.	-0.60	0.48
Phe	336	A	A	.	.	.	.	.	0.63	-0.03	.	*	.	0.30	0.54
Leu	337	A	A	.	.	.	.	.	0.78	-0.46	*	.	.	0.30	0.52
Ser	338	A	A	.	.	.	.	.	1.10	-0.46	*	.	F	0.94	1.24
Glu	339	A	A	.	.	.	.	.	0.80	-1.14	*	.	F	1.58	2.81
Asp	340	A	.	.	.	.	T	.	0.76	-1.54	*	*	F	2.32	4.57
Arg	341	A	.	.	.	.	T	.	1.57	-1.59	*	.	F	2.66	2.53
Arg	342	.	.	.	.	T	T	.	2.49	-1.97	*	.	F	3.40	2.86
Ser	343	.	.	.	.	T	T	.	2.44	-1.97	*	.	F	3.06	3.36
Val	344	.	.	.	.	T	.	.	2.23	-1.54	*	.	F	2.86	1.70
Arg	345	.	.	.	.	T	.	.	1.99	-1.11	*	*	F	2.86	1.34
Arg	346	.	.	.	.	T	.	.	1.99	-0.36	*	.	F	2.56	1.57
Gly	347	.	.	.	.	.	T	C	1.88	-0.74	*	*	F	2.86	4.13
Pro	348	.	.	.	.	T	T	.	2.29	-0.99	*	*	F	3.40	3.65
Tyr	349	.	.	.	.	T	T	.	2.29	-0.99	*	*	F	3.06	3.65
Arg	350	.	.	.	.	T	T	.	1.97	-0.34	.	*	F	2.42	2.74
Gln	351	.	.	B	B	.	.	.	1.86	-0.34	.	*	F	1.28	2.74
Arg	352	.	.	B	B	.	.	.	2.20	-0.77	.	*	F	1.24	2.92
Val	353	.	.	.	B	.	.	C	2.20	-1.13	.	*	F	1.10	2.40
Pro	354	.	.	.	B	.	.	C	2.44	-0.70	*	*	F	1.44	2.14
Asp	355	.	.	.	.	.	.	C	2.44	-1.10	*	*	F	1.98	1.89
Asn	356	.	.	.	.	.	T	C	1.74	-1.10	*	*	F	2.52	4.99
Pro	357	.	.	.	.	.	T	C	1.63	-0.96	*	*	F	2.86	2.80
Glu	358	.	.	.	.	T	T	.	2.19	-1.39	*	*	F	3.40	2.80
Arg	359	.	.	.	.	T	T	.	2.40	-1.00	*	*	F	3.06	2.33
Phe	360	.	.	.	.	T	T	.	2.19	-1.00	*	*	F	2.72	2.61
Asp	361	.	.	.	.	T	T	.	1.52	-1.00	.	*	F	2.38	2.33
Ser	362	.	.	.	.	T	T	.	0.88	-0.43	*	*	F	1.59	0.64
Gln	363	.	.	.	.	.	T	C	0.07	0.21	*	*	F	0.45	0.55
Pro	364	.	.	.	B	T	.	.	-0.39	0.11	.	*	F	0.25	0.27
Cys	365	.	.	.	B	T	.	.	0.02	0.54	.	*	.	-0.20	0.20
Val	366	.	.	.	B	.	.	C	0.02	1.07	.	.	.	-0.40	0.12
Leu	367	.	.	.	B	.	.	C	0.02	0.67	.	.	.	-0.40	0.14
Gly	368	.	.	.	B	T	.	.	-0.68	0.63	.	.	.	-0.20	0.34
Trp	369	A	.	.	.	.	.	.	-1.06	0.84	.	.	.	-0.40	0.40
Glu	370	A	.	.	.	.	.	.	-0.69	0.70	.	.	.	-0.40	0.48
Ser	371	A	.	.	.	.	.	.	-0.18	0.40	.	.	.	-0.40	0.66
Phe	372	A	.	.	.	.	.	.	0.68	0.40	.	.	.	-0.12	0.62
Ala	373	A	.	.	.	.	T	.	0.99	-0.51	.	.	F	1.71	0.71
Ser	374	.	.	.	.	T	T	.	1.03	-0.01	.	.	F	2.09	0.72
Gly	375	.	.	.	.	T	T	.	1.14	0.36	.	.	F	1.92	1.31
Lys	376	.	.	.	.	T	T	.	1.10	-0.43	.	*	F	2.80	2.54
His	377	.	.	.	.	.	.	C	1.80	-0.50	.	*	F	2.12	1.87
Tyr	378	.	.	.	.	.	T	C	1.69	-0.49	.	*	F	2.04	3.05
Arg	379	.	.	.	.	T	T	.	1.68	-0.13	*	*	F	1.96	1.32
Gly	380	.	.	.	.	T	T	.	2.02	0.36	*	*	F	1.08	1.40
Asn	381	.	.	.	.	T	T	.	1.69	-0.14	*	*	F	1.40	1.55
Phe	382	.	.	.	.	.	.	C	1.38	0.01	.	*	F	0.49	0.83
Thr	383	.	.	.	.	.	.	C	1.41	0.44	.	*	F	0.43	0.83
Glu	384	.	.	.	.	T	.	.	0.99	0.44	.	*	F	0.87	0.80
Trp	385	.	.	.	.	T	.	.	1.44	0.53	.	*	F	1.26	1.33
Gly	386	.	.	.	.	.	T	C	0.86	-0.26	.	*	F	2.40	1.81
Pro	387	.	.	.	.	.	T	C	1.31	-0.24	*	.	F	2.16	1.05
Thr	388	.	.	.	.	.	T	C	1.73	0.51	*	.	F	1.02	1.57
Arg	389	.	.	.	.	.	T	C	0.84	-0.40	*	.	F	1.68	3.11
Ala	390	.	.	.	B	T	.	.	1.13	-0.14	*	.	.	1.09	1.41
Tyr	391	.	.	.	B	T	.	.	1.18	-0.17	*	.	.	0.85	1.57
Arg	392	.	.	.	B	T	.	.	0.58	-0.27	.	.	.	0.85	1.07
Ile	393	.	.	.	B	T	.	.	0.89	0.41	.	.	.	-0.20	0.88
Asn	394	.	.	.	B	T	.	.	0.48	-0.09	*	.	.	0.70	0.93
Ser	395	.	.	.	.	T	.	.	1.07	-0.46	*	*	F	1.05	0.64
Leu	396	.	.	.	.	T	.	.	1.10	-0.06	.	*	F	1.54	1.58
Asp	397	.	.	.	.	T	.	.	0.32	-0.31	*	.	F	1.88	1.52
Ser	398	.	.	.	.	T	.	.	1.32	-0.14	*	.	F	2.07	0.61
Gln	399	.	.	.	.	.	T	C	1.37	-0.53	*	.	F	2.86	1.44
Pro	400	.	.	.	.	T	T	.	1.46	-1.21	*	.	F	3.40	1.73
Cys	401	.	.	.	.	T	T	.	1.98	-0.79	*	.	F	3.06	1.99
Arg	402	.	.	.	.	T	T	.	1.77	-0.26	*	.	F	2.42	1.21
Lys	403	.	.	.	.	T	.	.	1.77	-0.23	*	.	F	1.88	1.21
Pro	404	.	.	.	.	T	.	.	1.77	-0.27	*	.	F	1.54	3.03

Trp	405	.	.	.	.	.	T	C	1.98	-0.44	.	.	F	1.20	2.67
Pro	406	.	.	.	.	.	T	C	2.43	-0.04	.	.	F	1.20	2.32
Ser	407	.	.	.	.	T	T	.	2.11	0.39	.	.	F	1.08	2.32
Gln	408	.	.	.	.	T	T	.	2.03	0.39	.	.	F	1.36	3.41
Gln	409	.	.	.	.	.	.	C	2.24	-0.03	.	.	F	1.84	3.00
Pro	410	.	.	.	.	.	T	C	2.32	-0.06	.	.	F	2.32	3.60
Pro	411	.	.	.	.	T	T	.	2.32	-0.01	.	.	F	2.80	3.21
His	412	.	.	.	.	.	T	C	2.62	0.01	.	.	F	1.72	2.87
Asn	413	.	.	.	.	.	T	C	2.62	0.01	.	.	F	1.44	2.98
Pro	414	.	.	.	.	.	T	C	2.73	-0.41	.	.	F	1.76	3.34
Pro	415	.	.	.	.	.	T	C	2.91	-0.84	.	.	F	1.78	4.81
Asn	416	.	.	.	.	T	T	.	2.53	-0.84	.	.	F	1.70	4.07
Glu	417	A	.	.	.	.	T	.	1.76	-0.74	.	.	F	1.30	2.66
Arg	418	A	A	.	.	.	.	.	0.94	-0.49	.	.	F	0.60	1.42
His	419	A	A	.	.	.	.	.	0.94	-0.23	.	.	.	0.30	0.73
Ala	420	A	A	.	.	.	.	.	0.86	-0.20	.	.	.	0.30	0.65
Leu	421	A	A	.	.	.	.	.	0.51	0.19	.	.	.	-0.30	0.44
Leu	422	.	.	.	.	.	T	C	0.48	0.61	.	.	.	0.00	0.32
Pro	423	.	.	.	.	.	T	C	-0.49	0.61	*	*	F	0.15	0.44
Ser	424	.	.	.	.	T	T	.	-0.34	0.76	.	*	F	0.35	0.39
Gly	425	.	.	.	.	.	T	C	0.24	0.07	.	*	F	0.45	0.93
His	426	A	A	.	.	.	.	.	1.02	-0.61	.	*	F	0.90	1.04
Val	427	A	A	.	.	.	.	.	1.02	-0.54	.	*	.	0.75	1.06
Arg	428	A	A	.	.	.	.	.	1.02	-0.24	.	*	.	0.30	0.88
Glu	429	A	A	.	.	.	.	.	0.73	-0.24	*	*	.	0.45	1.00
His	430	A	A	.	.	.	.	.	0.49	-0.24	*	*	.	0.45	1.36
Leu	431	.	A	.	.	.	.	C	-0.18	-0.39	.	*	.	0.50	0.70
Pro	432	A	A	.	.	.	.	.	-0.02	0.40	.	*	.	-0.60	0.35
Ala	433	A	A	.	.	.	.	.	-0.44	1.19	.	*	.	-0.60	0.22
Ala	434	A	A	.	.	.	.	.	-0.66	1.17	.	.	.	-0.60	0.39
Phe	435	.	A	.	.	T	.	.	-0.93	0.91	.	.	.	-0.20	0.39
Phe	436	.	A	.	.	T	.	.	-0.33	0.97	.	.	.	-0.20	0.56
Thr	437	.	.	.	.	.	T	C	-0.71	0.90	.	.	F	0.15	0.86
Pro	438	.	.	.	.	.	T	C	-0.93	0.90	.	.	F	0.15	1.00
Thr	439	.	.	.	.	.	T	C	-1.01	0.80	.	.	F	0.15	0.95
Pro	440	.	.	.	.	T	T	.	-0.52	0.59	.	.	F	0.35	0.35
Ala	441	.	.	.	.	T	.	.	-0.12	0.53	.	.	.	0.00	0.35
Leu	442	.	.	.	.	.	.	C	-0.51	0.49	.	.	.	-0.20	0.33
Cys	443	.	.	B	.	.	T	.	-1.11	0.79	.	.	.	-0.20	0.18
Pro	444	A	.	.	.	.	T	.	-1.61	1.04	.	.	.	-0.20	0.15
Ser	445	A	.	.	.	.	T	.	-2.21	1.23	.	.	.	-0.20	0.15
Phe	446	A	.	.	.	.	T	.	-1.93	1.23	.	.	.	-0.20	0.23
Leu	447	A	.	.	B	.	.	.	-1.42	1.14	.	.	.	-0.60	0.22
Leu	448	A	.	.	B	.	.	.	-1.57	1.10	.	.	.	-0.60	0.22
Leu	449	A	.	.	B	.	.	.	-1.64	1.40	.	.	.	-0.60	0.21
Thr	450	A	.	.	B	.	.	.	-2.16	1.53	.	.	.	-0.60	0.26
Ser	451	A	.	.	B	.	.	.	-1.84	1.53	.	.	.	-0.60	0.26
Leu	452	A	.	.	B	.	.	.	-1.42	1.27	.	.	.	-0.60	0.41
Trp	453	A	.	.	B	.	.	.	-1.00	1.01	.	.	.	-0.60	0.36
Leu	454	A	.	.	B	.	.	.	-0.58	0.96	.	.	.	-0.60	0.34

Table 7

		I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Met	1	A	.	.	B	.	.	.	-0.29	-0.41	*	.	.	0.30	0.88
Arg	2	.	.	B	B	.	.	.	-0.19	-0.20	*	.	.	0.30	0.51
Glu	3	A	.	.	B	.	.	.	-0.04	0.29	.	*	.	-0.30	0.42
Ile	4	.	.	B	B	.	.	.	0.46	0.61	.	*	.	-0.60	0.67
Val	5	.	.	B	B	.	.	.	-0.01	0.00	.	*	.	0.30	0.67
Trp	6	.	.	B	B	.	.	.	0.28	0.64	.	*	.	-0.60	0.29
Tyr	7	.	.	B	B	.	.	.	0.17	1.13	.	.	.	-0.29	0.59
Arg	8	.	.	B	B	.	.	.	-0.18	0.44	*	.	.	0.17	1.32
Val	9	.	.	B	B	.	.	.	0.37	0.23	*	.	.	0.78	1.25
Thr	10	.	.	.	.	T	T	.	0.91	-0.26	*	*	F	2.49	0.79
Asp	11	.	.	.	.	T	T	.	0.31	-0.53	.	*	F	3.10	0.58
Gly	12	.	.	.	.	T	T	.	0.60	0.16	.	*	F	1.89	0.55
Gly	13	.	.	.	.	T	T	.	0.49	-0.49	.	*	F	2.18	0.76
Thr	14	.	.	.	B	.	.	C	1.39	-0.57	*	*	F	1.57	0.79
Ile	15	.	.	B	B	.	.	.	0.81	-0.57	*	*	F	1.21	1.59
Lys	16	.	.	B	B	.	.	.	0.11	-0.31	*	*	F	0.60	1.13

Gln	17	.	.	B	B	.	.	.	0.14	0.04	*	*	F	-0.15	0.68
Lys	18	.	.	B	B	.	.	.	-0.21	0.04	.	*	F	0.00	1.39
Ile	19	.	.	B	B	.	.	.	0.10	0.14	.	*	.	-0.30	0.60
Phe	20	.	.	B	B	.	.	.	0.40	0.14	.	*	.	-0.30	0.58
Thr	21	.	.	B	B	.	.	.	-0.24	0.24	.	*	.	-0.30	0.29
Phe	22	.	.	B	B	.	.	.	-0.94	0.86	.	.	.	-0.60	0.41
Asp	23	.	.	B	B	.	.	.	-1.29	0.96	.	.	.	-0.60	0.41
Ala	24	A	.	.	.	.	.	.	-0.71	0.56	.	*	.	-0.40	0.38
Met	25	A	.	.	.	.	.	.	-0.01	0.56	.	*	.	-0.40	0.64
Phe	26	A	.	.	.	.	.	.	0.06	0.17	.	*	.	-0.10	0.62
Ser	27	A	.	.	.	.	T	.	0.46	0.93	.	*	.	-0.20	0.96
Thr	28	A	.	.	.	.	T	.	0.42	0.81	.	.	.	-0.05	1.30
Asn	29	.	.	.	.	.	T	C	0.41	0.70	.	.	.	0.15	2.04
Tyr	30	.	.	.	.	.	T	C	1.01	0.53	.	.	.	0.15	1.50
Ser	31	.	.	.	.	.	.	C	1.71	0.14	.	.	.	0.25	1.81
His	32	A	.	.	.	.	.	.	1.77	0.06	.	.	.	0.05	1.81
Met	33	A	.	.	.	.	.	.	2.19	0.41	.	.	.	-0.25	1.81
Glu	34	A	.	.	.	.	.	.	2.23	-0.34	.	*	.	0.65	2.64
Asn	35	A	.	.	.	.	T	.	2.59	-0.73	.	.	.	1.15	3.88
Tyr	36	A	.	.	.	.	T	.	2.89	-1.23	.	*	F	1.30	7.67
Arg	37	A	.	.	.	.	T	.	2.92	-1.84	.	*	F	1.30	7.67
Lys	38	A	.	.	.	.	T	.	2.71	-1.84	.	*	F	1.30	7.97
Arg	39	A	.	.	.	.	.	.	1.86	-1.56	.	*	F	1.10	4.19
Glu	40	A	.	.	.	.	.	.	1.61	-1.67	.	*	F	1.10	1.59
Asp	41	.	.	B	B	.	.	.	1.86	-0.91	.	*	F	0.90	1.25
Leu	42	.	.	B	B	.	.	.	1.44	-0.51	.	*	.	0.75	1.10
Val	43	.	.	B	B	.	.	.	1.09	-0.13	.	.	.	0.30	0.85
Tyr	44	.	.	B	B	.	.	.	0.12	0.36	*	*	.	-0.30	0.74
Gln	45	.	.	B	B	.	.	.	0.23	1.00	*	*	F	-0.45	0.66
Ser	46	.	.	B	B	.	.	.	-0.58	0.31	*	*	F	0.00	1.75
Thr	47	.	.	B	B	.	.	.	0.02	0.36	*	*	F	-0.15	0.92
Val	48	.	.	B	B	.	.	.	0.88	0.03	*	*	F	-0.15	0.82
Arg	49	.	.	B	B	.	.	.	0.27	-0.37	.	*	.	0.45	1.06
Leu	50	.	.	B	B	.	.	.	0.38	-0.11	.	*	.	0.30	0.55
Pro	51	.	.	B	B	.	.	.	-0.21	-0.60	.	*	.	0.75	1.44
Glu	52	.	.	B	B	.	.	.	-0.20	-0.56	.	*	.	0.60	0.52
Val	53	.	.	B	B	.	.	.	0.66	-0.17	.	*	.	0.61	0.84
Arg	54	.	.	B	B	.	.	.	0.54	-0.86	.	*	.	1.22	0.91
Ile	55	.	.	B	B	.	.	.	1.01	-0.89	.	*	F	1.68	0.84
Ser	56	.	.	.	.	T	T	.	1.01	-0.46	*	*	F	2.64	1.12
Asp	57	.	.	.	.	T	T	.	0.77	-0.67	*	*	F	3.10	0.88
Asn	58	.	.	.	.	.	T	C	1.62	0.09	*	*	F	1.84	1.98
Gly	59	.	.	.	.	.	T	C	0.84	-0.60	*	*	F	2.43	2.56
Pro	60	.	.	.	.	T	.	.	1.70	-0.41	.	*	F	1.67	0.82
Tyr	61	.	.	.	.	T	.	.	1.14	0.09	.	.	.	0.61	0.69
Glu	62	.	.	B	B	.	.	.	0.80	0.33	.	*	.	-0.30	0.52
Cys	63	.	.	B	B	.	.	.	-0.09	0.33	.	*	.	-0.30	0.33
His	64	.	.	B	B	.	.	.	0.01	0.59	.	.	.	-0.60	0.15
Val	65	.	.	B	B	.	.	.	0.22	0.59	.	*	.	-0.60	0.13
Gly	66	.	.	B	B	.	.	.	0.58	0.59	*	*	.	-0.60	0.42
Ile	67	.	.	B	B	.	.	.	-0.01	0.01	*	*	.	-0.30	0.60
Tyr	68	.	A	B	.	.	.	.	0.34	0.01	*	*	.	-0.30	0.82
Asp	69	A	A	.	.	.	.	.	0.49	-0.14	*	.	F	0.60	1.20
Arg	70	A	A	.	.	.	.	.	1.34	-0.57	*	.	F	0.90	3.35
Ala	71	A	A	.	.	.	.	.	1.73	-1.26	*	.	F	0.90	3.71
Thr	72	A	A	.	.	.	.	.	1.77	-2.01	*	.	F	0.90	4.44
Arg	73	A	A	.	.	.	.	.	1.16	-1.37	*	.	F	0.90	1.68
Glu	74	A	A	.	B	.	.	.	0.34	-0.73	*	.	F	0.90	1.24
Lys	75	.	A	B	B	.	.	.	-0.36	-0.54	*	.	F	0.75	0.71
Val	76	.	A	B	B	.	.	.	-0.07	-0.53	.	.	.	0.60	0.36
Val	77	.	A	B	B	.	.	.	-0.10	-0.14	.	*	.	0.30	0.28
Leu	78	.	A	B	B	.	.	.	-0.21	0.29	.	*	.	-0.30	0.14
Ala	79	.	.	B	.	.	T	.	-1.10	0.69	*	.	.	-0.20	0.30
Ser	80	A	.	.	.	.	T	.	-1.84	0.73	*	.	F	-0.05	0.29
Gly	81	A	.	.	.	.	T	.	-1.80	0.87	.	*	F	-0.05	0.30
Asn	82	A	.	.	.	.	T	.	-0.94	0.87	.	*	.	-0.20	0.24
Ile	83	.	.	B	B	.	.	.	-0.99	0.77	.	*	.	-0.60	0.29
Phe	84	.	.	B	B	.	.	.	-1.00	1.03	.	*	.	-0.60	0.22
Leu	85	.	.	B	B	.	.	.	-1.29	1.21	.	*	.	-0.60	0.14
Asn	86	.	.	B	B	.	.	.	-1.16	1.31	*	*	.	-0.60	0.20
Val	87	.	.	B	B	.	.	.	-1.37	1.06	.	*	.	-0.60	0.35
Met	88	.	.	B	B	.	.	.	-0.79	0.70	.	.	.	-0.60	0.65
Ala	89	.	.	.	B	.	.	C	-0.39	0.50	.	.	.	-0.40	0.59

Pro	90	.	.	.	.	.	T	C	-0.47	0.49	.	*	F	0.30	1.06
Pro	91	.	.	.	.	.	T	C	-0.47	0.53	.	*	F	0.15	0.75
Thr	92	A	.	.	.	.	T	.	-0.47	-0.09	.	.	F	1.00	1.29
Ser	93	A	.	.	.	.	T	.	-0.72	0.06	.	.	F	0.25	0.62
Ile	94	.	A	B	B	.	.	.	-0.72	0.27	.	.	.	-0.30	0.30
Glu	95	.	A	B	B	.	.	.	-1.10	0.34	.	.	.	-0.30	0.21
Val	96	.	A	B	B	.	.	.	-0.89	0.36	.	.	.	-0.30	0.16
Val	97	.	A	B	B	.	.	.	-0.89	-0.03	.	.	.	0.30	0.37
Ala	98	.	A	B	B	.	.	.	-0.80	-0.23	.	.	.	0.30	0.31
Ala	99	.	A	B	.	.	.	.	-0.50	0.20	.	.	.	-0.30	0.65
Asp	100	A	A	.	.	.	.	.	-0.71	0.06	.	.	F	-0.15	0.88
Thr	101	.	A	.	.	.	.	C	-0.56	-0.16	.	.	F	0.80	1.35
Pro	102	.	.	.	.	.	.	C	0.00	0.13	*	.	F	0.40	1.16
Ala	103	.	.	.	.	.	.	C	0.70	0.01	*	.	F	0.25	0.93
Pro	104	.	.	.	.	.	.	C	1.04	0.01	*	.	F	0.40	1.26
Phe	105	.	.	B	.	.	.	.	1.04	0.29	.	.	.	0.05	1.28
Ser	106	.	.	B	.	.	T	.	0.77	0.26	.	*	.	0.34	2.19
Arg	107	.	.	B	.	.	T	.	0.98	0.26	.	.	.	0.43	1.43
Tyr	108	.	.	B	.	.	T	.	1.57	0.23	*	.	.	0.52	2.86
Gln	109	.	.	.	.	T	T	.	1.08	-0.16	*	.	.	1.61	3.43
Ala	110	.	.	.	.	T	.	.	1.47	0.24	*	.	.	0.90	1.52
Gln	111	.	.	.	B	T	.	.	0.96	0.73	*	*	.	0.31	1.40
Asn	112	.	.	.	B	T	.	.	-0.01	0.66	*	*	.	0.07	0.66
Phe	113	.	.	B	B	.	.	.	-0.43	0.90	.	.	.	-0.42	0.49
Thr	114	.	.	B	B	.	.	.	-1.32	0.97	.	.	.	-0.51	0.15
Leu	115	.	.	B	B	.	.	.	-1.59	1.26	.	.	.	-0.60	0.07
Val	116	.	.	B	B	.	.	.	-1.89	1.50	.	.	.	-0.60	0.06
Cys	117	.	.	B	B	.	.	.	-2.23	1.10	.	.	.	-0.60	0.05
Ile	118	.	.	B	B	.	.	.	-1.88	1.04	.	.	.	-0.39	0.06
Val	119	.	.	B	.	.	T	.	-1.52	0.79	.	.	.	0.22	0.08
Ser	120	.	.	.	.	T	T	.	-0.92	0.14	*	.	F	1.28	0.31
Gly	121	.	.	.	.	T	T	.	-0.66	0.00	.	.	F	2.09	0.69
Gly	122	.	.	.	.	.	T	C	-0.20	-0.19	.	.	F	2.10	0.94
Lys	123	.	.	.	.	.	.	C	0.09	-0.40	*	.	F	1.84	1.08
Pro	124	.	.	.	.	.	.	C	0.09	-0.17	.	.	F	1.63	1.08
Ala	125	.	.	B	.	.	.	.	0.14	0.04	.	.	F	0.47	0.81
Pro	126	.	.	B	.	.	.	.	-0.21	0.37	.	*	.	0.11	0.64
Met	127	.	A	B	.	.	.	.	0.18	1.16	.	.	.	-0.60	0.36
Val	128	.	A	B	.	.	.	.	0.24	0.73	.	.	.	-0.60	0.71
Tyr	129	.	A	B	.	.	.	.	0.46	0.23	.	.	.	0.04	0.89
Phe	130	.	A	B	.	.	.	.	0.70	-0.20	*	.	.	1.13	1.51
Lys	131	.	.	B	.	.	T	.	0.91	-0.39	*	.	.	1.87	2.01
Arg	132	.	.	.	.	T	T	.	1.30	-1.03	*	.	F	3.06	2.23
Asp	133	.	.	.	.	T	T	.	1.27	-1.36	*	.	F	3.40	3.97
Gly	134	.	.	.	.	.	T	C	1.51	-1.46	*	.	F	2.86	1.39
Glu	135	.	.	.	.	.	.	C	1.62	-1.46	*	.	F	2.32	1.19
Pro	136	.	.	.	.	.	.	C	0.72	-0.96	*	.	F	1.83	0.72
Ile	137	.	.	B	.	.	.	.	0.40	-0.31	*	.	F	0.99	0.54
Asp	138	.	.	B	.	.	.	.	-0.41	-0.31	.	.	.	0.50	0.48
Ala	139	.	.	B	.	.	.	.	-0.37	0.37	.	.	.	-0.10	0.26
Val	140	.	.	B	.	.	.	.	-0.37	0.33	.	.	.	-0.10	0.49
Pro	141	.	.	B	.	.	.	.	-0.37	-0.36	.	.	.	0.50	0.51
Leu	142	.	.	B	.	.	.	.	0.31	0.07	.	.	.	0.14	0.78
Ser	143	.	.	B	.	.	.	.	-0.28	0.00	.	.	F	1.28	1.62
Glu	144	.	.	B	.	.	.	.	-0.28	-0.14	.	.	F	1.52	1.06
Pro	145	.	.	.	.	.	.	C	0.28	-0.07	.	.	F	1.96	1.30
Pro	146	.	.	.	.	T	.	.	0.19	-0.37	.	.	F	2.40	1.30
Ala	147	.	.	.	.	T	.	.	0.66	-0.37	.	.	F	2.16	1.00
Ala	148	.	.	.	.	.	.	C	0.74	0.06	.	.	F	0.97	0.64
Ser	149	.	.	.	.	.	T	C	-0.07	0.06	.	.	F	0.93	0.64
Ser	150	.	.	B	.	.	T	.	0.14	0.31	.	.	F	0.49	0.52
Gly	151	.	.	B	.	.	T	.	0.36	0.21	.	.	F	0.51	0.90
Pro	152	.	.	.	.	.	T	C	0.64	-0.29	.	.	F	1.72	1.12
Leu	153	.	.	.	.	.	.	C	1.34	-0.29	.	.	F	1.78	1.12
Gln	154	.	.	B	.	.	.	.	1.43	-0.67	*	.	F	2.14	2.22
Asp	155	.	.	B	.	.	T	.	1.03	-0.67	*	.	F	2.60	2.22
Ser	156	.	.	B	.	.	T	.	1.49	-0.31	*	.	F	2.04	2.33
Arg	157	.	.	B	.	.	T	.	1.40	-1.00	*	.	F	2.08	2.64
Pro	158	.	.	B	.	.	T	.	1.40	-1.01	*	.	F	1.82	2.11
Phe	159	.	A	.	.	T	.	.	0.59	-0.33	*	.	F	1.26	1.30
Arg	160	.	A	B	.	.	.	.	0.56	-0.03	*	.	F	0.45	0.55
Ser	161	.	A	B	.	.	.	.	0.97	0.47	*	.	.	-0.60	0.48
Leu	162	.	A	B	.	.	.	.	0.86	0.04	*	.	.	-0.15	1.09

Leu	163	.	A	B	.	.	.	.	0.26	-0.74	*	*	.	0.60	0.93
His	164	A	A	.	.	.	.	.	0.96	-0.06	*	.	.	0.30	0.57
Arg	165	A	A	.	.	.	.	.	0.84	-0.44	*	.	F	0.60	1.16
Asp	166	A	A	.	.	.	.	.	0.83	-1.13	*	.	F	0.90	2.35
Leu	167	A	A	.	.	.	.	.	1.69	-1.33	*	.	F	0.90	2.49
Asp	168	A	.	.	.	.	T	.	1.90	-1.83	*	.	F	1.30	2.54
Asp	169	A	.	.	.	.	T	.	1.93	-1.21	.	.	F	1.30	1.51
Thr	170	A	.	.	.	.	T	.	1.87	-0.81	.	.	F	1.30	3.16
Lys	171	A	.	.	.	.	T	.	1.57	-1.50	.	.	F	1.30	3.79
Met	172	A	A	.	.	.	.	.	1.57	-1.11	.	.	F	0.90	3.04
Gln	173	A	A	.	.	.	.	.	1.27	-0.43	.	*	F	0.60	1.74
Lys	174	A	A	.	.	.	.	.	0.46	-0.53	*	*	F	0.90	1.16
Ser	175	A	A	.	.	.	.	.	-0.04	0.16	*	.	F	-0.15	0.97
Leu	176	.	A	B	.	.	.	.	-0.09	0.23	*	.	.	-0.30	0.46
Ser	177	.	A	B	.	.	.	.	-0.08	-0.17	.	.	.	0.30	0.39
Leu	178	.	A	B	.	.	.	.	-0.08	0.33	.	.	.	-0.30	0.29
Leu	179	A	A	.	.	.	.	.	-0.12	-0.06	*	*	.	0.30	0.61
Asp	180	A	A	.	.	.	.	.	0.29	-0.34	*	*	.	0.64	0.73
Ala	181	A	A	.	.	.	.	.	0.76	-0.73	*	*	F	1.58	1.74
Glu	182	A	A	.	.	.	.	.	0.71	-0.99	*	.	F	1.92	2.09
Asn	183	.	.	.	.	T	T	.	1.63	-1.24	*	.	F	3.06	1.24
Arg	184	.	.	.	.	T	T	.	2.23	-1.24	*	*	F	3.40	2.40
Gly	185	.	.	.	.	T	T	.	1.99	-1.31	*	.	F	3.06	2.14
Gly	186	.	.	.	.	T	T	.	2.27	-0.56	*	.	F	2.72	2.09
Arg	187	.	.	.	.	.	T	C	2.27	-0.47	*	.	F	1.88	1.54
Pro	188	.	.	.	.	.	T	C	2.38	-0.47	*	.	F	1.54	2.69
Tyr	189	.	.	B	.	.	T	.	2.06	-0.90	*	.	F	1.64	5.33
Thr	190	.	.	B	.	.	T	.	2.10	-0.90	*	.	F	1.98	4.20
Glu	191	.	.	B	.	.	.	.	2.56	-0.51	*	.	F	2.12	3.64
Arg	192	.	.	B	.	.	T	.	2.10	-0.94	*	.	F	2.66	4.55
Pro	193	.	.	.	.	T	T	.	1.50	-1.27	*	.	F	3.40	3.12
Ser	194	.	.	.	.	T	T	.	1.43	-1.07	*	.	F	3.06	1.49
Arg	195	.	.	.	.	T	T	.	1.53	-0.59	*	.	F	2.92	1.10
Gly	196	.	.	.	.	T	.	.	1.53	-0.16	*	.	F	2.28	1.10
Leu	197	.	.	.	.	.	.	C	1.21	-0.59	*	.	F	2.24	1.37
Thr	198	.	.	.	.	.	.	C	1.42	-0.54	*	*	F	2.10	1.08
Pro	199	.	.	.	.	.	.	C	0.83	-0.14	*	.	F	2.00	1.75
Asp	200	.	.	.	.	.	T	C	-0.09	0.11	*	*	F	1.40	1.49
Pro	201	.	.	B	.	.	T	.	-0.56	0.11	.	*	F	0.85	0.85
Asn	202	.	.	B	.	.	T	.	0.26	0.31	.	*	.	0.50	0.45
Ile	203	.	.	B	.	.	T	.	0.36	0.29	.	*	.	0.30	0.47
Leu	204	.	.	B	.	.	.	.	0.26	0.71	.	*	.	-0.40	0.47
Leu	205	.	.	B	.	.	.	.	-0.06	0.77	.	*	.	-0.40	0.42
Gln	206	.	.	B	.	.	T	.	0.16	0.86	.	*	F	-0.05	0.87
Pro	207	.	.	B	.	.	T	.	0.16	0.17	.	*	F	0.66	1.83
Thr	208	.	.	.	.	.	T	C	0.16	-0.11	.	.	F	1.72	3.56
Thr	209	.	.	.	.	.	T	C	0.76	-0.11	*	.	F	1.98	1.44
Glu	210	.	.	.	.	.	.	C	1.57	-0.09	*	.	F	2.04	1.44
Asn	211	.	.	.	.	.	.	C	1.26	-0.51	*	.	F	2.60	1.73
Ile	212	.	.	B	B	.	.	.	0.61	-0.51	*	.	F	1.94	1.73
Pro	213	.	.	B	B	.	.	.	0.07	-0.36	*	.	F	1.23	0.74
Glu	214	.	.	B	B	.	.	.	0.08	0.29	*	.	F	0.37	0.34
Thr	215	.	.	B	B	.	.	.	0.19	0.27	.	.	F	0.11	0.65
Val	216	.	.	B	B	.	.	.	0.19	-0.41	*	.	F	0.45	0.83
Val	217	.	.	B	B	.	.	.	0.38	-0.84	.	.	.	0.60	0.83
Ser	218	.	.	B	.	.	.	.	0.38	-0.06	*	.	.	0.50	0.50
Arg	219	.	.	B	.	.	.	.	0.49	-0.11	*	*	F	0.80	1.04
Glu	220	A	.	.	.	.	.	.	0.51	-0.76	*	.	F	1.10	2.73
Phe	221	A	.	.	.	.	T	.	0.51	-0.49	*	.	F	1.00	2.14
Pro	222	A	.	.	.	.	T	.	1.33	-0.23	*	.	F	0.85	0.81
Arg	223	.	.	.	.	T	T	.	1.33	0.27	*	.	.	0.50	0.64
Trp	224	.	.	.	.	T	T	.	0.63	0.66	*	.	.	0.20	0.99
Val	225	.	.	.	B	.	.	C	0.63	0.37	*	.	.	-0.10	0.65
His	226	.	.	.	B	.	.	C	1.12	-0.06	*	.	.	0.50	0.57
Ser	227	.	.	.	B	.	.	C	1.02	0.37	*	*	.	-0.10	0.84
Ala	228	.	.	.	.	.	.	C	0.67	-0.06	*	.	F	1.00	1.63
Glu	229	.	.	.	.	.	T	C	0.26	0.06	.	.	F	0.60	1.88
Pro	230	.	.	.	.	T	T	.	0.30	0.34	.	*	F	0.80	1.21
Thr	231	.	.	.	.	T	T	.	0.44	0.64	.	*	F	0.35	0.99
Tyr	232	A	.	.	.	.	T	.	0.71	0.14	.	*	.	0.42	1.12
Phe	233	.	.	B	B	.	.	.	1.00	0.64	*	.	.	-0.26	0.99
Leu	234	.	.	B	B	.	.	.	1.11	0.60	*	.	.	-0.09	0.92
Arg	235	.	.	B	B	.	.	.	1.01	0.11	*	.	.	0.53	1.15

His	236	.	.	B	.	.	T	.	1.11	-0.16	*	.	.	1.70	1.91
Ser	237	.	.	.	.	T	T	.	1.06	-0.51	*	.	F	2.38	3.58
Arg	238	.	.	.	.	.	T	C	1.46	-0.81	*	.	F	2.01	2.45
Thr	239	.	.	.	.	.	T	C	2.27	-0.43	*	.	F	1.54	2.41
Pro	240	.	.	.	.	.	.	C	1.81	-0.93	*	.	F	1.74	3.01
Ser	241	.	.	.	.	T	T	.	1.53	-0.89	.	.	F	2.24	1.52
Ser	242	.	.	.	.	.	T	C	0.98	-0.40	.	*	F	2.01	1.52
Asp	243	.	.	.	.	.	T	C	0.87	-0.24	.	*	F	2.13	0.73
Gly	244	.	.	.	.	.	T	C	0.32	-0.67	.	*	F	2.70	0.94
Thr	245	.	.	B	B	.	.	.	0.64	-0.41	.	*	F	1.53	0.52
Val	246	.	.	B	B	.	.	.	0.36	-0.80	.	*	F	1.56	0.61
Glu	247	.	.	B	B	.	.	.	-0.16	-0.30	*	*	.	0.84	0.62
Val	248	.	.	B	B	.	.	.	-0.97	-0.04	.	*	.	0.57	0.36
Arg	249	.	.	B	B	.	.	.	-0.93	0.16	*	*	.	-0.30	0.40
Ala	250	.	.	B	B	.	.	.	-0.91	0.00	.	*	.	0.30	0.33
Leu	251	A	.	.	B	.	.	.	-0.37	0.91	.	*	.	-0.60	0.47
Leu	252	A	.	.	B	.	.	.	-1.18	0.76	*	*	.	-0.60	0.34
Thr	253	.	.	.	B	T	.	.	-0.32	1.44	*	*	.	-0.20	0.28
Trp	254	.	.	B	B	.	.	.	-0.64	1.34	*	*	.	-0.60	0.55
Thr	255	.	.	B	B	.	.	.	-0.06	1.09	.	*	.	-0.45	1.03
Leu	256	.	.	.	B	.	.	C	-0.13	0.80	.	*	.	0.05	1.24
Asn	257	.	.	.	.	.	T	C	0.68	1.00	.	*	.	0.60	0.82
Pro	258	.	.	.	.	.	T	C	0.99	0.09	.	*	F	1.35	0.95
Gln	259	.	.	.	.	.	T	C	1.28	0.00	.	*	F	2.40	1.86
Ile	260	.	.	.	.	.	T	C	1.00	-0.69	.	*	F	3.00	2.00
Asp	261	A	A	.	.	.	.	.	1.00	-0.59	.	*	F	2.10	1.31
Asn	262	A	A	.	.	.	.	.	0.30	-0.33	.	*	F	1.35	0.62
Glu	263	A	A	.	.	.	.	.	0.21	0.06	.	*	F	0.45	0.77
Ala	264	A	A	.	.	.	.	.	-0.46	-0.24	.	*	.	0.60	0.62
Leu	265	A	A	.	.	.	.	.	0.43	0.33	.	*	.	-0.30	0.21
Phe	266	A	A	.	.	.	.	.	-0.42	-0.07	.	*	.	0.30	0.21
Ser	267	A	A	.	.	.	.	.	-0.38	0.57	.	*	.	-0.60	0.15
Cys	268	A	A	.	.	.	.	.	-0.41	0.07	.	*	.	-0.30	0.37
Glu	269	A	A	.	.	.	.	.	-0.03	-0.11	.	*	.	0.30	0.58
Val	270	A	A	.	.	.	.	.	0.19	-0.47	.	*	.	0.30	0.66
Lys	271	A	A	.	.	.	.	.	0.08	-0.36	.	*	.	0.45	1.25
His	272	A	A	.	.	.	.	.	0.08	-0.24	.	.	.	0.30	0.60
Pro	273	A	A	.	.	.	.	.	0.14	0.14	.	.	.	-0.15	1.08
Ala	274	A	A	.	.	.	.	.	-0.07	0.11	.	.	.	-0.30	0.53
Leu	275	A	A	.	.	.	.	.	0.19	0.54	.	.	.	-0.60	0.61
Ser	276	A	A	.	.	.	.	.	0.14	0.66	.	*	.	-0.60	0.39
Met	277	A	A	.	.	.	.	.	-0.41	0.63	.	*	.	-0.60	0.66
Pro	278	A	A	.	.	.	.	.	-0.20	0.63	.	*	.	-0.60	0.81
Met	279	A	A	.	.	.	.	.	-0.47	-0.06	.	*	.	0.45	1.05
Gln	280	A	A	.	.	.	.	.	0.03	0.20	.	*	.	-0.30	0.79
Ala	281	A	.	.	B	.	.	.	-0.48	0.07	.	*	.	-0.30	0.74
Glu	282	A	.	.	B	.	.	.	-0.73	0.33	.	*	.	-0.30	0.61
Val	283	A	.	.	B	.	.	.	-1.11	0.36	.	*	.	-0.30	0.26
Thr	284	A	.	.	B	.	.	.	-0.72	0.46	.	*	.	-0.60	0.26
Leu	285	A	.	.	B	.	.	.	-0.68	0.39	.	*	.	-0.30	0.23
Val	286	A	.	.	B	.	.	.	-0.43	0.39	.	.	.	0.00	0.63
Ala	287	A	.	.	.	.	T	.	-0.64	0.17	*	.	.	0.70	0.43
Pro	288	A	.	.	.	.	T	.	0.26	0.11	*	.	F	1.15	0.81
Lys	289	.	.	.	.	T	T	.	-0.32	-0.57	*	.	F	2.90	2.19
Gly	290	.	.	.	.	.	T	C	-0.37	-0.53	*	.	F	3.00	1.52
Pro	291	.	.	B	B	.	.	.	-0.11	-0.39	*	.	F	1.65	0.73
Lys	292	.	.	B	B	.	.	.	0.17	-0.20	*	.	F	1.35	0.36
Ile	293	.	.	B	B	.	.	.	0.17	0.29	*	.	.	0.30	0.53
Val	294	.	.	B	B	.	.	.	-0.18	0.29	*	.	.	0.00	0.53
Met	295	.	.	B	B	.	.	.	0.28	0.24	*	.	.	-0.04	0.35
Thr	296	.	.	B	.	.	T	.	-0.10	0.24	.	*	F	0.77	0.99
Pro	297	.	.	B	.	.	T	.	-0.03	0.06	.	*	F	1.18	1.34
Ser	298	.	.	B	.	.	T	.	0.00	-0.59	.	*	F	2.34	2.66
Arg	299	.	.	B	.	.	T	.	0.51	-0.56	.	*	F	2.60	1.37
Ala	300	.	.	B	B	.	.	.	1.11	-0.61	.	*	F	1.79	0.87
Arg	301	.	.	B	B	.	.	.	1.11	-1.04	.	*	F	1.68	1.09
Val	302	.	.	B	B	.	.	.	0.47	-0.94	.	*	.	1.12	0.80
Gly	303	.	.	B	B	.	.	.	0.88	-0.30	.	*	F	0.71	0.59
Asp	304	.	.	B	B	.	.	.	-0.12	-0.80	*	*	F	0.75	0.59
Thr	305	.	.	B	B	.	.	.	-0.34	-0.11	*	*	F	0.45	0.56
Val	306	.	.	B	B	.	.	.	-1.31	-0.07	*	*	.	0.30	0.46
Arg	307	.	.	B	B	.	.	.	-0.49	0.14	*	*	.	-0.30	0.21
Ile	308	.	.	B	B	.	.	.	-0.49	0.64	*	*	.	-0.60	0.19

Leu	309	.	.	B	B	.	.	.	-1.19	0.59	*	*	.	-0.60	0.26
Val	310	.	.	B	B	.	.	.	-0.88	0.73	*	*	.	-0.60	0.11
His	311	.	.	B	.	.	T	.	-0.02	1.13	*	*	.	-0.20	0.28
Gly	312	.	.	.	.	.	T	C	-0.13	0.84	*	*	.	0.00	0.55
Phe	313	.	.	.	.	.	T	C	-0.10	0.16	.	.	.	0.45	1.29
Gln	314	.	.	.	.	.	T	C	0.01	0.16	*	.	F	0.69	0.70
Asn	315	.	.	.	.	.	.	C	0.66	0.44	.	.	F	0.43	0.62
Glu	316	.	.	.	.	.	.	C	0.69	0.44	.	.	F	0.82	1.10
Val	317	.	.	.	.	.	.	C	0.82	-0.34	.	.	F	1.96	1.10
Phe	318	.	.	.	.	.	T	C	0.92	-0.31	.	.	F	2.40	1.06
Pro	319	.	.	.	.	.	T	C	0.22	-0.10	.	.	F	2.01	0.60
Glu	320	.	.	.	.	.	T	C	-0.09	0.69	.	.	F	0.87	0.70
Pro	321	A	.	.	.	.	T	.	-0.38	0.53	.	.	F	0.58	1.17
Met	322	A	.	.	B	.	.	.	0.17	0.66	*	.	.	-0.36	0.80
Phe	323	A	.	.	B	.	.	.	0.98	0.71	*	.	.	-0.60	0.67
Thr	324	A	.	.	B	.	.	.	0.33	0.71	*	.	.	-0.60	0.84
Trp	325	.	.	B	B	.	.	.	-0.01	0.93	*	.	.	-0.39	0.63
Thr	326	.	.	B	B	.	.	.	-0.10	0.74	*	*	.	-0.18	0.72
Arg	327	.	.	B	B	.	.	.	0.61	0.34	*	*	F	0.48	0.67
Val	328	.	.	.	B	T	.	.	0.50	-0.14	*	*	F	1.84	1.25
Gly	329	.	.	.	.	.	T	C	0.00	-0.37	*	*	F	2.10	0.71
Ser	330	.	.	B	.	.	T	.	0.29	-0.17	*	*	F	1.69	0.30
Arg	331	.	.	B	.	.	T	.	0.26	-0.17	*	*	F	1.48	0.68
Leu	332	.	.	B	.	.	T	.	-0.16	-0.39	*	*	F	1.27	0.68
Leu	333	.	.	.	.	.	T	C	0.11	-0.43	*	.	F	1.26	0.68
Asp	334	.	.	.	.	.	T	C	0.46	-0.31	*	*	F	1.05	0.35
Gly	335	.	.	.	.	.	T	C	0.06	-0.31	*	*	F	1.05	0.73
Ser	336	A	.	.	.	.	T	.	-0.06	-0.21	*	*	F	0.85	0.77
Ala	337	A	.	.	.	.	.	.	0.41	-0.90	.	*	F	0.95	0.77
Glu	338	A	.	.	.	.	.	.	1.27	-0.47	.	*	F	0.65	0.77
Phe	339	A	.	.	.	.	T	.	1.27	-0.90	.	*	F	1.30	1.15
Asp	340	A	.	.	.	.	T	.	0.80	-1.29	.	*	F	1.30	1.97
Gly	341	A	.	.	.	.	T	.	0.24	-1.10	.	*	F	1.15	0.94
Lys	342	A	.	.	.	.	T	.	0.02	-0.46	.	*	F	0.85	0.80
Glu	343	A	A	.	.	.	.	.	0.02	-0.56	.	*	F	0.75	0.40
Leu	344	A	A	.	.	.	.	.	0.83	-0.56	*	*	.	0.60	0.69
Val	345	A	A	.	.	.	.	.	-0.02	-0.99	.	.	.	0.60	0.68
Leu	346	A	A	.	.	.	.	.	0.11	-0.34	.	.	.	0.30	0.29
Glu	347	A	A	.	.	.	.	.	-0.52	0.09	.	*	.	-0.30	0.55
Arg	348	A	A	.	.	.	.	.	-0.52	-0.10	*	*	.	0.30	0.74
Val	349	A	A	.	.	.	.	.	-0.52	-0.74	*	*	.	0.75	1.56
Pro	350	A	A	.	.	.	.	.	0.33	-0.74	*	*	.	0.60	0.74
Ala	351	A	.	.	.	.	.	.	0.80	-0.34	*	*	.	0.50	0.61
Glu	352	A	.	.	.	.	.	.	0.50	0.09	*	*	.	-0.10	0.81
Leu	353	A	.	.	.	.	T	.	-0.21	-0.17	*	*	F	0.85	0.71
Asn	354	.	.	.	.	T	T	.	0.40	0.01	*	*	F	0.65	0.69
Gly	355	.	.	.	.	T	T	.	0.72	0.27	*	*	F	0.65	0.63
Ser	356	.	.	.	.	T	T	.	0.64	0.27	*	*	.	0.65	1.48
Met	357	.	.	B	.	.	.	.	0.33	0.16	*	*	.	-0.10	0.49
Tyr	358	.	.	B	.	.	.	.	0.56	0.24	*	*	.	-0.10	0.72
Arg	359	.	.	B	.	.	.	.	0.56	0.31	.	.	.	-0.10	0.54
Cys	360	.	.	B	.	.	.	.	0.90	0.33	*	.	.	-0.10	0.95
Thr	361	.	.	B	.	.	.	.	0.99	0.11	.	*	.	-0.10	0.98
Ala	362	.	.	B	.	.	.	.	0.78	-0.21	.	*	F	0.65	0.77
Gln	363	.	.	B	.	.	.	.	0.68	0.47	.	*	F	-0.10	1.19
Asn	364	.	.	.	.	.	T	C	0.27	0.33	.	*	F	0.45	0.81
Pro	365	.	.	.	.	.	T	C	0.62	0.23	.	.	F	0.60	1.08
Leu	366	.	.	.	.	T	T	.	0.93	0.21	.	.	F	0.65	0.90
Gly	367	.	.	.	.	T	T	.	1.21	-0.19	.	.	F	1.51	0.93
Ser	368	.	.	.	.	.	T	C	1.18	-0.10	.	.	F	1.57	0.87
Thr	369	.	.	B	.	.	T	.	0.87	-0.03	.	*	F	1.78	1.44
Asp	370	.	.	B	.	.	T	.	1.19	-0.23	.	*	F	2.04	2.10
Thr	371	.	.	B	.	.	T	.	1.19	-0.66	*	*	F	2.60	3.07
His	372	.	.	B	B	.	.	.	0.64	-0.36	*	*	F	1.64	1.75
Thr	373	.	.	B	B	.	.	.	0.09	-0.16	.	*	F	1.23	0.74
Arg	374	.	.	B	B	.	.	.	-0.30	0.49	.	*	.	-0.08	0.38
Leu	375	.	.	B	B	.	.	.	-0.30	0.79	.	*	.	-0.34	0.24
Ile	376	.	.	B	B	.	.	.	0.01	0.29	.	.	.	-0.30	0.29
Val	377	.	.	B	B	.	.	.	-0.17	0.20	.	.	.	-0.30	0.24
Phe	378	.	.	B	B	.	.	.	0.14	0.63	.	.	.	-0.60	0.44
Glu	379	.	.	B	B	.	.	.	-0.86	0.34	.	.	F	0.00	1.02
Asn	380	.	.	.	.	.	T	C	-0.26	0.34	*	.	F	0.45	0.96
Pro	381	.	.	.	.	T	T	.	0.74	0.13	*	.	F	1.14	1.72

		I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Asn	382	.	.	.	.	.	T	C	1.26	-0.66	.	.	F	2.18	1.95
Ile	383	.	.	.	.	.	T	C	1.64	-0.23	.	.	F	2.22	1.20
Pro	384	.	.	.	.	.	T	C	1.64	-0.14	*	.	F	2.56	1.12
Arg	385	.	.	.	.	T	T	.	1.64	-0.57	*	.	F	3.40	1.20
Gly	386	.	.	B	.	.	T	.	1.56	-0.97	*	.	F	2.66	2.87
Thr	387	.	.	B	.	.	T	.	1.56	-1.27	*	.	F	2.63	2.49
Glu	388	.	.	B	.	.	.	.	2.10	-1.30	*	.	F	2.40	2.04
Asp	389	.	.	.	.	T	T	.	2.01	-0.87	*	*	F	2.97	2.04
Ser	390	.	.	.	.	T	T	.	1.01	-0.91	*	*	F	2.94	1.89
Asn	391	.	.	.	.	T	T	.	1.01	-0.71	.	.	F	3.10	0.77
Gly	392	.	.	.	.	T	T	.	1.11	-0.29	.	.	F	2.49	0.45
Ser	393	.	.	.	.	T	.	.	0.80	0.14	.	.	F	1.38	0.52
Ile	394	.	.	.	.	.	.	C	0.46	0.24	.	.	F	0.87	0.47
Gly	395	.	.	.	.	.	T	C	0.17	0.27	*	.	F	0.76	0.47
Pro	396	.	.	.	.	.	T	C	0.28	0.34	*	*	F	0.45	0.35
Thr	397	.	.	B	.	.	T	.	-0.19	-0.04	*	*	F	0.85	0.99
Gly	398	.	.	B	.	.	T	.	-0.20	-0.04	*	*	F	0.85	0.83
Ala	399	.	.	B	B	.	.	.	-0.12	0.01	*	*	F	-0.15	0.77
Arg	400	.	.	B	B	.	.	.	-0.63	0.27	.	*	.	-0.30	0.44
Leu	401	.	.	B	B	.	.	.	-1.23	0.43	.	*	.	-0.60	0.33
Thr	402	.	.	B	B	.	.	.	-1.51	0.69	.	*	.	-0.60	0.27
Leu	403	.	.	B	B	.	.	.	-1.98	0.69	.	*	.	-0.60	0.14
Val	404	.	.	B	B	.	.	.	-1.70	1.37	.	*	.	-0.60	0.14
Leu	405	A	.	.	B	.	.	.	-2.67	1.17	.	*	.	-0.60	0.14
Ala	406	A	.	.	B	.	.	.	-2.74	1.33	.	.	.	-0.60	0.13
Leu	407	A	.	.	B	.	.	.	-3.24	1.33	.	.	.	-0.60	0.12
Thr	408	A	.	.	B	.	.	.	-2.43	1.37	.	*	.	-0.60	0.12
Val	409	A	.	.	B	.	.	.	-2.39	0.69	.	*	.	-0.60	0.20
Ile	410	A	.	.	B	.	.	.	-1.89	0.87	.	*	.	-0.60	0.20
Leu	411	A	.	.	B	.	.	.	-1.69	0.67	*	.	.	-0.60	0.20
Glu	412	A	.	.	B	.	.	.	-1.27	0.61	.	*	.	-0.60	0.35
Leu	413	A	.	.	B	.	.	.	-1.34	0.40	.	.	.	-0.30	0.64
Thr	414	A	.	.	B	.	.	.	-0.88	0.14	.	.	.	-0.30	0.99

Table 8

		I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Met	1	A	A	.	.	.	.	.	-0.04	-0.17	.	.	.	0.45	1.00
Glu	2	A	A	.	.	.	.	.	-0.24	-0.10	.	.	.	0.30	0.79
Pro	3	A	A	.	.	.	.	.	-0.67	-0.03	.	.	.	0.30	0.63
Ala	4	A	A	.	.	.	.	.	-0.31	0.23	.	*	.	-0.30	0.52
Ala	5	A	A	.	.	.	.	.	-0.62	0.11	.	*	.	-0.30	0.41
Ala	6	A	A	.	.	.	.	.	-0.32	0.90	.	.	.	-0.60	0.23
Leu	7	A	A	.	.	.	.	.	-0.21	0.86	*	.	.	-0.60	0.30
His	8	A	A	.	.	.	.	.	-0.21	0.36	*	.	.	-0.30	0.59
Phe	9	A	A	.	.	.	.	.	-0.21	0.29	*	.	.	-0.30	0.90
Ser	10	A	A	.	.	.	.	.	0.08	0.29	*	.	.	-0.15	1.11
Arg	11	A	.	.	.	.	T	.	-0.14	-0.01	*	.	F	1.00	1.09
Pro	12	A	.	.	.	.	T	.	-0.14	0.17	*	.	F	0.40	1.04
Ala	13	A	.	.	.	.	T	.	-0.92	0.07	*	.	F	0.25	0.64
Ser	14	A	.	.	.	.	T	.	-1.03	0.37	*	.	.	0.10	0.27
Leu	15	A	.	.	B	.	.	.	-1.54	1.06	*	.	.	-0.60	0.14
Leu	16	A	.	.	B	.	.	.	-1.96	1.31	.	*	.	-0.60	0.12
Leu	17	A	.	.	B	.	.	.	-2.56	1.20	.	.	.	-0.60	0.12
Leu	18	A	.	.	B	.	:	.	-2.63	1.50	.	.	.	-0.60	0.12
Leu	19	A	.	.	B	.	.	.	-2.92	1.39	.	.	.	-0.60	0.08
Ser	20	A	.	.	B	.	.	.	-2.92	1.20	.	.	.	-0.60	0.09
Leu	21	A	.	.	B	.	.	.	-2.97	1.20	.	.	.	-0.60	0.09
Cys	22	A	.	.	B	.	.	.	-2.46	1.16	.	*	.	-0.60	0.08
Ala	23	A	.	.	B	.	.	.	-2.23	0.86	.	*	.	-0.60	0.08
Leu	24	A	.	.	B	.	.	.	-1.42	0.97	.	*	.	-0.60	0.10
Val	25	A	.	.	B	.	.	.	-1.98	0.69	.	*	.	-0.60	0.33
Ser	26	A	.	.	B	.	.	.	-1.48	0.76	.	*	.	-0.60	0.24
Ala	27	.	.	B	B	.	.	.	-1.67	0.74	.	*	.	-0.60	0.43
Gln	28	.	.	B	B	.	.	.	-1.93	0.70	.	*	.	-0.60	0.43
Val	29	.	.	B	B	.	.	.	-1.47	0.70	.	*	.	-0.60	0.24
Thr	30	.	.	B	B	.	.	.	-0.82	0.74	.	*	.	-0.60	0.23
Val	31	.	.	B	B	.	.	.	-0.83	0.67	.	*	.	-0.60	0.21
Val	32	.	.	B	B	.	.	.	-0.24	0.76	.	*	.	-0.60	0.40
Gly	33	.	.	B	.	.	T	.	-0.46	0.11	.	.	F	0.25	0.47

Pro	34	.	.	.	.	.	T	C	-0.49	0.06	.	.	F	0.45	0.97
Thr	35	.	.	.	.	.	T	C	-0.99	0.10	.	.	F	0.45	0.92
Asp	36	.	.	.	.	.	T	C	-0.72	0.14	.	.	F	0.45	0.76
Pro	37	.	.	B	B	.	.	.	-0.47	0.21	.	.	F	-0.15	0.50
Ile	38	.	.	B	B	.	.	.	-0.98	0.40	.	.	.	-0.30	0.34
Leu	39	.	.	B	B	.	.	.	-1.11	0.56	*	.	.	-0.60	0.15
Ala	40	.	.	B	B	.	.	.	-0.80	0.99	*	.	.	-0.60	0.10
Met	41	.	.	B	B	.	.	.	-0.80	0.56	*	.	.	-0.60	0.24
Val	42	.	.	B	B	.	.	.	-0.90	0.27	.	.	.	-0.30	0.47
Gly	43	A	.	.	.	.	T	.	-0.32	0.07	.	.	F	0.25	0.67
Glu	44	A	.	.	.	.	T	.	-0.32	0.06	*	*	F	0.25	0.98
Asn	45	.	.	.	.	T	T	.	0.38	0.13	*	*	F	0.80	1.09
Thr	46	.	.	.	.	T	T	.	0.31	-0.51	.	*	F	1.70	2.15
Thr	47	A	.	.	B	.	.	.	0.50	-0.37	.	*	F	0.45	0.66
Leu	48	.	.	B	B	.	.	.	0.03	0.20	*	*	.	-0.30	0.22
Arg	49	.	.	B	B	.	.	.	-0.27	0.49	*	*	.	-0.60	0.13
Cys	50	.	.	B	B	.	.	.	-0.48	0.39	*	*	.	0.00	0.12
Cys	51	.	.	B	B	.	.	.	-0.17	0.33	*	*	.	0.30	0.22
Leu	52	.	.	.	B	.	.	C	0.14	-0.36	*	*	.	1.40	0.19
Ser	53	.	.	.	.	.	T	C	0.96	-0.36	*	*	F	2.25	0.63
Pro	54	.	.	.	.	.	T	C	0.26	-0.53	*	*	F	3.00	1.89
Glu	55	A	.	.	.	.	T	.	0.92	-0.60	.	.	F	2.50	2.31
Glu	56	A	.	.	.	.	T	.	1.59	-1.29	.	.	F	2.20	2.99
Asn	57	A	A	.	.	.	.	.	1.80	-1.67	.	.	F	1.50	3.23
Ala	58	A	A	.	.	.	.	.	2.10	-1.49	.	.	F	1.20	1.85
Glu	59	A	A	.	.	.	.	.	1.46	-1.49	*	*	F	0.90	1.85
Asp	60	A	A	.	.	.	.	.	1.57	-0.84	*	*	F	0.75	0.85
Met	61	A	A	.	.	.	.	.	1.28	-1.24	*	*	.	0.75	1.65
Glu	62	A	A	.	.	.	.	.	0.58	-0.83	*	*	.	0.75	1.00
Val	63	A	A	.	.	.	.	.	1.17	-0.04	*	*	.	0.30	0.52
Arg	64	A	A	.	.	.	.	.	0.87	0.36	*	*	.	-0.30	0.91
Trp	65	A	A	.	.	.	.	.	0.87	0.13	*	*	.	-0.30	0.70
Phe	66	A	A	.	.	.	.	.	0.77	0.53	*	*	.	-0.45	1.64
Gln	67	A	A	.	.	.	.	.	0.47	0.67	*	*	F	-0.45	0.73
Ser	68	.	.	.	.	.	T	C	1.11	1.06	*	.	F	0.15	0.93
Gln	69	.	.	.	.	T	T	.	0.41	0.57	*	*	F	0.50	1.65
Phe	70	.	.	.	.	.	T	C	-0.16	0.29	.	*	F	0.45	0.96
Ser	71	.	.	.	.	.	T	C	-0.16	0.53	.	*	F	0.15	0.53
Pro	72	.	.	.	B	.	.	C	-1.01	0.93	.	*	.	-0.40	0.27
Ala	73	.	.	B	B	.	.	.	-0.96	1.17	.	.	.	-0.60	0.23
Val	74	.	.	B	B	.	.	.	-0.91	1.14	.	.	.	-0.60	0.27
Phe	75	.	.	B	B	.	.	.	-0.56	0.76	.	.	.	-0.60	0.35
Val	76	.	.	B	B	.	.	.	-0.60	0.76	*	.	.	-0.30	0.34
Tyr	77	.	.	B	.	.	T	.	-0.28	0.69	*	.	.	0.40	0.45
Lys	78	.	.	.	.	T	T	.	0.31	0.04	.	*	F	1.70	1.02
Gly	79	.	.	.	.	.	T	C	1.28	-0.74	.	*	F	2.70	2.39
Gly	80	.	.	.	.	.	T	C	1.67	-1.39	*	*	F	3.00	2.98
Arg	81	.	A	.	.	.	.	C	2.52	-1.66	*	*	F	2.30	2.15
Glu	82	A	A	.	.	.	.	.	2.77	-1.66	.	*	F	1.80	3.77
Arg	83	A	A	.	.	.	.	.	2.72	-2.09	*	*	F	1.50	6.59
Thr	84	A	A	.	.	.	.	.	3.11	-2.11	.	*	F	1.20	5.83
Glu	85	A	A	.	.	.	.	.	3.46	-2.11	.	*	F	0.90	6.73
Glu	86	A	A	.	.	.	.	.	3.34	-2.11	.	*	F	0.90	5.95
Gln	87	A	A	.	.	.	.	.	3.10	-2.11	.	*	F	0.90	7.14
Lys	88	A	A	.	.	.	.	.	3.10	-1.84	.	*	F	0.90	6.46
Glu	89	A	A	.	.	.	.	.	3.07	-1.84	.	*	F	1.24	7.31
Glu	90	A	A	.	.	.	.	.	3.18	-1.41	.	*	F	1.58	4.18
Tyr	91	A	.	.	.	.	T	.	2.87	-1.81	.	*	F	2.32	4.09
Arg	92	A	.	.	.	.	T	.	2.56	-1.33	*	*	F	2.66	3.41
Gly	93	.	.	.	.	T	T	.	1.81	-0.84	*	*	F	3.40	2.84
Arg	94	A	.	.	.	.	T	.	0.96	-0.06	.	*	F	2.36	1.57
Thr	95	.	.	B	B	.	.	.	0.66	-0.17	.	*	F	1.47	0.59
Thr	96	.	.	B	B	.	.	.	0.94	0.21	.	*	F	0.53	0.81
Phe	97	.	.	B	B	.	.	.	0.83	-0.21	.	*	.	0.98	0.82
Val	98	.	.	B	B	.	.	.	0.88	-0.21	.	*	.	0.98	0.95
Ser	99	.	.	B	B	.	.	.	0.88	-0.31	.	*	F	1.47	0.88
Lys	100	.	.	B	.	.	.	.	0.84	-0.80	*	*	F	2.46	2.00
Asp	101	.	.	.	.	T	T	.	0.86	-1.16	*	*	F	3.40	2.67
Ser	102	.	.	.	.	T	T	.	0.70	-1.41	*	*	F	3.06	2.67
Arg	103	.	.	.	.	T	T	.	0.97	-1.16	*	*	F	2.57	0.99
Gly	104	A	.	.	.	.	T	.	0.46	-0.66	*	*	F	1.83	0.60
Ser	105	A	.	.	B	.	.	.	-0.48	0.03	*	*	F	0.19	0.37
Val	106	.	.	B	B	.	.	.	-1.37	0.33	.	*	.	-0.30	0.13

Ala	107	.	.	B	B	.	.	.	-1.10	1.01	.	*	.	-0.60	0.09
Leu	108	.	.	B	B	.	.	.	-1.21	1.09	*	*	.	-0.60	0.09
Ile	109	.	.	B	B	.	.	.	-1.72	1.10	*	.	.	-0.60	0.21
Ile	110	.	.	B	B	.	.	.	-1.73	1.10	*	.	.	-0.60	0.15
His	111	.	.	B	B	.	.	.	-1.47	1.09	*	.	.	-0.60	0.26
Asn	112	.	.	B	B	.	.	.	-0.88	0.90	.	.	.	-0.26	0.38
Val	113	.	.	B	B	.	.	.	-0.07	0.21	.	.	.	0.38	0.94
Thr	114	.	.	B	B	.	.	.	0.82	-0.47	.	.	.	1.47	1.15
Ala	115	.	.	.	B	.	.	C	1.37	-0.57	*	.	F	2.46	1.15
Glu	116	.	.	.	.	T	T	.	0.51	-0.54	.	.	F	3.40	1.54
Asp	117	.	.	.	.	T	T	.	0.27	-0.50	.	*	F	2.91	0.75
Asn	118	.	.	.	.	T	T	.	1.12	-0.23	*	.	F	2.42	1.16
Gly	119	.	.	.	.	T	T	.	0.77	-0.33	.	.	F	2.08	1.16
Ile	120	.	.	.	B	T	.	.	1.11	0.24	.	.	.	0.44	0.37
Tyr	121	.	.	B	B	.	.	.	0.41	1.00	.	.	.	-0.60	0.36
Gln	122	.	.	B	B	.	.	.	0.41	1.39	.	.	.	-0.60	0.32
Cys	123	.	.	B	B	.	.	.	0.41	1.36	*	.	.	-0.60	0.78
Tyr	124	.	.	B	B	.	.	.	0.41	0.67	*	.	.	-0.60	0.87
Phe	125	.	.	B	B	.	.	.	1.41	0.34	*	.	.	0.01	0.49
Gln	126	.	.	B	B	.	.	.	1.36	-0.06	*	.	F	1.22	1.81
Glu	127	.	.	.	B	T	.	.	0.69	-0.24	*	.	F	1.93	1.55
Gly	128	.	.	.	.	T	T	.	1.36	-0.43	*	.	F	2.49	0.96
Arg	129	.	.	.	.	T	T	.	1.60	-0.81	*	.	F	3.10	0.89
Ser	130	.	.	.	.	T	T	.	1.71	-1.21	*	.	F	2.79	0.89
Cys	131	A	.	.	.	.	T	.	0.82	-0.71	*	.	F	2.08	0.91
Asn	132	A	A	.	.	.	.	.	0.01	-0.46	*	*	.	0.92	0.32
Glu	133	A	A	.	.	.	.	.	0.32	0.23	*	*	.	0.01	0.20
Ala	134	A	A	.	.	.	.	.	-0.60	0.34	*	.	.	-0.30	0.51
Ile	135	A	A	.	.	.	.	.	-1.16	0.46	*	.	.	-0.60	0.26
Leu	136	A	A	.	.	.	.	.	-1.34	0.70	.	.	.	-0.60	0.11
His	137	A	A	.	.	.	.	.	-1.93	1.34	.	.	.	-0.60	0.08
Leu	138	A	A	.	.	.	.	.	-1.93	1.34	.	.	.	-0.60	0.12
Val	139	A	A	.	.	.	.	.	-1.34	0.66	.	.	.	-0.60	0.24
Val	140	A	A	.	.	.	.	.	-0.49	0.37	.	.	.	-0.30	0.30
Ala	141	A	A	.	.	.	.	.	0.32	0.37	.	.	.	-0.30	0.50
Asp	142	A	A	.	.	.	.	.	0.14	0.09	.	.	.	-0.08	1.09
Gln	143	.	A	B	.	.	.	.	0.14	-0.13	.	.	F	0.74	2.27
His	144	.	A	.	.	.	.	C	0.70	-0.09	.	.	F	1.01	1.85
Asn	145	.	.	.	.	.	T	C	1.27	-0.20	*	.	F	1.48	1.48
Pro	146	.	.	.	.	T	T	.	0.97	0.71	.	.	F	0.70	0.90
Leu	147	.	.	.	.	T	T	.	0.76	1.00	.	.	.	0.48	0.46
Ser	148	.	.	.	.	T	T	.	-0.13	0.93	.	.	.	0.41	0.45
Trp	149	.	.	B	B	.	.	.	-0.31	1.21	.	.	.	-0.46	0.20
Ile	150	.	.	B	B	.	.	.	-0.31	1.21	.	.	.	-0.53	0.38
Pro	151	.	.	B	B	.	.	.	-0.44	0.93	.	.	.	-0.60	0.49
Ile	152	.	.	B	B	.	.	.	0.06	0.97	.	.	F	-0.45	0.46
Pro	153	.	.	B	.	.	T	.	-0.46	0.54	.	.	F	-0.05	0.95
Gln	154	.	.	.	.	T	T	.	-0.47	0.54	.	.	F	0.35	0.51
Gly	155	.	.	.	.	.	T	C	-0.39	0.50	.	*	F	0.15	0.97
Thr	156	.	.	B	.	.	T	.	-0.57	0.50	*	*	F	-0.05	0.52
Leu	157	.	.	B	B	.	.	.	-0.07	0.50	*	*	.	-0.60	0.38
Ser	158	.	.	B	B	.	.	.	-0.24	0.53	.	*	.	-0.60	0.49
Leu	159	.	.	B	B	.	.	.	-0.63	0.53	.	*	.	-0.60	0.44

Table 9

		I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV
Met	1	A	A	.	.	.	.	.	-1.47	0.70	.	.	.	-0.60	0.31
Ala	2	A	A	.	.	.	.	.	-1.38	0.96	.	.	.	-0.60	0.20
Leu	3	A	A	.	.	.	.	.	-1.80	0.91	.	.	.	-0.60	0.21
Met	4	A	A	.	.	.	.	.	-2.27	1.17	.	.	.	-0.60	0.17
Leu	5	A	A	.	.	.	.	.	-2.69	1.20	.	.	.	-0.60	0.13
Ser	6	A	A	.	.	.	.	.	-2.39	1.39	.	.	.	-0.60	0.13
Leu	7	A	A	.	.	.	.	.	-2.61	1.09	.	.	.	-0.60	0.17
Val	8	A	A	.	.	.	.	.	-2.61	1.16	*	.	.	-0.60	0.17
Leu	9	A	A	.	.	.	.	.	-1.97	1.16	*	.	.	-0.60	0.11
Ser	10	A	A	.	.	.	.	.	-1.97	0.77	*	.	.	-0.60	0.26
Leu	11	.	A	B	.	.	.	.	-2.01	0.77	*	.	.	-0.60	0.28
Leu	12	.	A	B	.	.	.	.	-1.50	0.56	*	.	.	-0.60	0.34
Lys	13	.	A	B	.	.	.	.	-0.99	0.26	*	.	F	-0.15	0.34

Leu	14	.	A	.	.	.	.	C	-0.18	0.30	.	.	F	0.05	0.41
Gly	15	.	.	.	.	T	T	.	-0.17	0.01	*	.	F	0.65	0.86
Ser	16	.	.	.	.	.	T	C	0.64	0.24	*	.	F	0.45	0.45
Gly	17	.	.	.	.	.	T	C	0.60	0.64	*	.	F	0.15	0.95
Gln	18	.	.	B	.	.	T	.	-0.14	0.60	*	.	F	-0.05	0.71
Trp	19	.	.	B	B	.	.	.	0.32	0.96	.	.	.	-0.60	0.46
Gln	20	.	.	B	B	.	.	.	0.46	1.00	.	*	.	-0.60	0.46
Val	21	.	.	B	B	.	.	.	0.76	1.00	.	.	.	-0.60	0.41
Phe	22	.	.	B	B	.	.	.	1.14	0.60	.	.	.	-0.30	0.65
Gly	23	.	.	.	.	.	T	C	0.93	-0.31	.	.	.	1.50	0.75
Pro	24	.	.	.	.	T	T	.	0.37	-0.29	.	.	F	2.30	1.57
Asp	25	.	.	.	.	.	T	C	0.37	-0.29	.	.	F	2.40	1.34
Lys	26	.	.	.	.	.	T	C	0.63	-0.67	*	.	F	3.00	2.35
Pro	27	.	.	.	B	.	.	C	0.52	-0.60	*	.	F	2.30	1.54
Val	28	.	.	B	B	.	.	.	0.01	-0.34	*	.	.	1.20	0.76
Gln	29	.	.	B	B	.	.	.	-0.12	0.30	*	.	.	0.30	0.28
Ala	30	.	.	B	B	.	.	.	-0.12	0.73	.	.	.	-0.30	0.18
Leu	31	.	.	B	B	.	.	.	-0.17	0.30	.	.	.	-0.30	0.42
Val	32	.	.	B	B	.	.	.	-0.54	-0.34	.	.	.	0.30	0.41
Gly	33	A	.	.	B	.	.	.	-0.28	-0.24	.	.	F	0.45	0.41
Glu	34	A	A	.	.	.	.	.	-0.98	-0.24	.	.	F	0.45	0.50
Asp	35	A	A	.	.	.	.	.	-0.69	-0.14	.	.	F	0.45	0.58
Ala	36	A	A	.	.	.	.	.	-0.54	-0.40	.	.	.	0.30	0.79
Ala	37	A	A	.	B	.	.	.	-0.39	-0.26	.	.	.	0.30	0.24
Phe	38	A	A	.	B	.	.	.	-0.86	0.53	.	.	.	-0.60	0.13
Ser	39	A	A	.	B	.	.	.	-1.16	1.21	.	.	.	-0.60	0.10
Cys	40	A	A	.	B	.	.	.	-1.37	1.10	.	.	.	-0.60	0.14
Phe	41	A	A	.	B	.	.	.	-0.73	1.03	.	.	.	-0.60	0.24
Leu	42	.	A	.	B	.	.	C	-0.46	0.24	.	.	.	-0.10	0.36
Ser	43	.	.	.	.	.	T	C	0.24	0.34	.	*	F	0.45	0.98
Pro	44	.	.	.	.	.	T	C	-0.04	0.17	.	*	F	0.60	1.82
Lys	45	.	.	.	.	.	T	C	0.62	-0.11	.	*	F	1.20	2.23
Thr	46	A	.	.	.	.	T	.	0.73	-0.80	.	*	F	1.30	2.88
Asn	47	A	A	.	.	.	.	.	0.94	-0.69	.	*	F	0.90	1.88
Ala	48	A	A	.	.	.	.	.	1.24	-0.50	.	.	.	0.30	0.93
Glu	49	A	A	.	.	.	.	.	0.60	-0.50	.	*	.	0.45	1.12
Ala	50	A	A	.	.	.	.	.	0.67	-0.34	.	*	.	0.30	0.52
Met	51	A	A	.	.	.	.	.	0.28	-0.74	*	*	.	0.60	1.00
Glu	52	A	A	.	.	.	.	.	-0.42	-0.46	*	.	.	0.30	0.50
Val	53	A	A	.	.	.	.	.	0.28	0.33	*	.	.	-0.30	0.43
Arg	54	A	A	.	.	.	.	.	-0.07	-0.17	*	.	.	0.30	0.85
Phe	55	A	A	.	.	.	.	.	0.52	-0.36	*	*	.	0.30	0.48
Phe	56	A	.	.	.	.	T	.	0.42	0.04	*	*	.	0.25	1.13
Arg	57	A	.	.	.	.	T	.	0.12	0.19	*	*	.	0.10	0.50
Gly	58	.	.	.	.	T	T	.	0.68	0.57	*	.	F	0.35	0.77
Gln	59	.	.	.	.	T	T	.	-0.29	0.17	*	*	F	0.80	1.20
Phe	60	.	.	.	B	.	.	C	-0.44	0.03	*	*	F	0.05	0.45
Ser	61	.	.	.	B	.	.	C	0.22	0.67	*	*	F	-0.25	0.34
Ser	62	.	.	B	B	.	.	.	-0.70	0.74	*	*	.	-0.60	0.27
Val	63	.	.	B	B	.	.	.	-0.60	1.03	*	.	.	-0.60	0.25
Val	64	.	.	B	B	.	.	.	-0.49	1.00	*	.	.	-0.60	0.30
His	65	.	.	B	B	.	.	.	0.21	0.61	*	.	.	-0.26	0.43
Leu	66	.	.	B	B	.	.	.	0.17	0.23	*	.	.	0.38	0.98
Tyr	67	.	.	B	.	.	T	.	0.51	0.01	*	.	.	1.27	1.30
Arg	68	.	.	.	.	T	T	.	1.37	-0.63	*	.	F	3.06	1.92
Asp	69	.	.	.	.	T	T	.	2.22	-1.13	*	.	F	3.40	3.88
Gly	70	.	.	.	.	T	T	.	2.04	-1.41	*	.	F	3.06	4.29
Lys	71	.	.	.	.	T	.	.	2.16	-1.74	*	.	F	2.52	3.39
Asp	72	.	.	.	.	.	.	C	1.80	-0.96	.	.	F	1.98	1.76
Gln	73	.	.	.	.	.	.	C	1.69	-0.34	.	.	F	1.34	1.76
Pro	74	.	.	B	.	.	.	.	1.09	-0.37	.	.	F	0.80	1.52
Phe	75	.	.	B	.	.	.	.	1.22	0.24	.	.	.	-0.10	0.90
Met	76	.	.	B	.	.	.	.	1.18	0.67	.	.	.	-0.40	0.80
Gln	77	.	.	B	.	.	.	.	0.93	0.67	.	.	.	-0.40	0.90
Met	78	.	.	B	.	.	.	.	0.93	1.00	*	.	.	-0.25	1.63
Pro	79	.	.	B	.	.	.	.	0.80	0.61	*	*	.	0.09	2.85
Gln	80	.	.	.	.	T	.	.	1.61	0.43	*	*	F	0.98	1.63
Tyr	81	.	.	.	.	T	T	.	1.90	0.03	.	*	F	1.82	3.23
Gln	82	A	.	.	.	.	T	.	1.94	-0.10	.	*	F	2.36	3.01
Gly	83	.	.	.	.	T	T	.	1.73	-0.53	.	*	F	3.40	3.48
Arg	84	.	.	B	.	.	T	.	1.09	-0.24	.	*	F	2.36	1.83
Thr	85	.	.	B	.	.	.	.	1.13	-0.36	.	*	F	1.90	0.78
Lys	86	.	.	B	.	.	.	.	1.38	-0.76	.	*	F	2.24	1.59

Leu	87	.	.	B	.	.	.	.	1.08	-1.19	.	*	F	2.13	1.35
Val	88	.	.	B	.	.	T	.	0.53	-0.80	.	*	F	2.22	1.26
Lys	89	.	.	B	.	.	T	.	-0.17	-0.60	.	.	F	2.30	0.44
Asp	90	.	.	B	.	.	T	.	0.14	-0.10	*	.	F	1.77	0.54
Ser	91	.	.	B	.	.	T	.	-0.24	-0.79	*	.	.	1.84	1.26
Ile	92	A	A	.	.	.	.	.	0.68	-1.00	*	*	.	1.06	0.62
Ala	93	A	A	.	.	.	.	.	0.64	-1.00	.	*	F	0.98	0.73
Glu	94	A	A	.	.	.	.	.	0.30	-0.31	.	*	F	0.45	0.38
Gly	95	A	A	.	.	.	.	.	-0.51	-0.31	*	*	F	0.45	0.73
Arg	96	A	A	.	.	.	.	.	-0.10	-0.31	*	*	F	0.45	0.60
Ile	97	A	A	.	.	.	.	.	-0.02	-0.81	.	*	F	0.75	0.67
Ser	98	A	A	.	.	.	.	.	0.57	-0.13	*	*	.	0.30	0.56
Leu	99	A	A	.	.	.	.	.	0.57	-0.56	*	*	.	0.60	0.50
Arg	100	A	A	.	.	.	.	.	0.02	-0.16	*	*	.	0.45	1.14
Leu	101	A	A	.	.	.	.	.	-0.40	-0.16	*	*	.	0.30	0.60
Glu	102	.	A	B	.	.	.	.	-0.37	-0.06	.	*	.	0.45	1.04
Asn	103	.	A	B	.	.	.	.	-0.88	-0.10	.	*	.	0.30	0.40
Ile	104	.	A	B	.	.	.	.	-0.07	0.59	.	*	.	-0.60	0.40
Thr	105	.	A	B	.	.	.	.	-0.77	-0.10	.	.	.	0.30	0.38
Val	106	.	A	B	.	.	.	.	-0.30	0.40	.	.	.	-0.60	0.24
Leu	107	.	A	B	.	.	.	.	-1.11	0.43	.	.	.	-0.60	0.34
Asp	108	.	A	B	.	.	.	.	-1.36	0.43	.	.	.	-0.60	0.19
Ala	109	.	A	B	.	.	.	.	-0.81	0.70	.	.	.	-0.60	0.41
Gly	110	.	.	.	.	T	.	.	-1.17	0.49	*	.	.	0.00	0.49
Leu	111	.	.	B	.	.	T	.	-0.20	0.37	*	.	.	0.10	0.16
Tyr	112	.	.	B	.	.	T	.	-0.28	0.37	*	*	.	0.10	0.30
Gly	113	.	.	B	.	.	T	.	-0.58	0.56	*	.	.	-0.20	0.22
Cys	114	.	.	B	.	.	T	.	-0.29	0.51	*	*	.	-0.20	0.35
Arg	115	.	.	B	B	.	.	.	0.06	0.21	*	*	.	-0.30	0.30
Ile	116	.	.	B	B	.	.	.	0.57	-0.14	.	*	F	0.45	0.52
Ser	117	.	.	B	B	.	.	.	0.57	-0.19	*	*	F	0.76	1.31
Ser	118	.	.	B	.	.	T	.	0.67	0.00	*	*	F	1.32	1.05
Gln	119	.	.	B	.	.	T	.	1.33	0.76	.	*	F	0.58	2.35
Ser	120	.	.	.	.	T	T	.	1.27	0.47	.	*	F	1.14	3.03
Tyr	121	.	.	.	.	T	T	.	1.57	0.09	.	.	F	1.60	4.52
Tyr	122	.	A	.	.	T	.	.	0.98	0.20	.	.	.	0.89	2.64
Gln	123	.	A	B	.	.	.	.	0.99	0.49	.	.	.	0.03	1.38
Lys	124	.	A	B	.	.	.	.	0.99	1.01	*	.	.	-0.28	0.93
Ala	125	.	A	B	.	.	.	.	0.48	0.26	*	.	.	0.01	1.02
Ile	126	.	A	B	.	.	.	.	0.72	0.19	.	*	.	-0.30	0.49
Trp	127	.	A	B	.	.	.	.	0.11	0.19	.	*	.	-0.30	0.42
Glu	128	A	A	.	.	.	.	.	-0.19	0.83	*	*	.	-0.60	0.31
Leu	129	A	A	.	.	.	.	.	-0.82	0.71	*	*	.	-0.60	0.59
Gln	130	.	A	B	.	.	.	.	-1.04	0.53	.	*	.	-0.60	0.57
Val	131	.	A	B	.	.	.	.	-0.50	0.30	.	*	.	-0.30	0.27
Ser	132	.	A	.	.	.	.	C	-0.51	0.73	.	*	.	-0.40	0.33
Ala	133	.	A	.	.	.	.	C	-1.37	0.43	.	*	.	-0.40	0.25
Leu	134	.	A	B	.	.	.	.	-0.77	0.67	.	*	.	-0.60	0.25
Gly	135	.	A	.	.	T	.	.	-1.58	0.46	.	.	.	-0.20	0.29
Ser	136	.	.	B	B	.	.	.	-1.61	0.76	.	.	.	-0.60	0.24
Val	137	.	.	B	B	.	.	.	-1.61	0.94	.	.	.	-0.60	0.20
Pro	138	.	.	B	B	.	.	.	-1.91	0.64	.	.	.	-0.60	0.27
Leu	139	.	.	B	B	.	.	.	-1.41	0.90	.	.	.	-0.60	0.14
Ile	140	.	.	B	B	.	.	.	-1.41	1.00	.	.	.	-0.60	0.28
Ser	141	.	.	B	B	.	.	.	-1.36	0.79	.	.	.	-0.60	0.18
Ile	142	.	.	B	B	.	.	.	-1.36	1.11	.	*	.	-0.60	0.34
Thr	143	.	.	B	B	.	.	.	-1.14	1.07	*	.	.	-0.60	0.36
Gly	144	.	.	B	B	.	.	.	-0.22	0.39	*	.	.	-0.04	0.45
Tyr	145	.	.	B	B	.	.	.	0.67	0.00	*	*	.	0.97	1.25
Val	146	.	.	B	B	.	.	.	0.08	-0.69	*	.	F	1.68	1.44
Asp	147	.	.	B	.	.	T	.	0.97	-0.49	*	*	F	2.04	1.02
Arg	148	.	.	B	.	.	T	.	0.47	-0.51	*	.	F	2.60	1.13
Asp	149	.	.	B	.	.	T	.	0.00	-0.59	*	.	F	2.34	1.25
Ile	150	.	.	B	.	.	T	.	-0.42	-0.54	*	.	.	1.78	0.62
Gln	151	.	A	B	.	.	.	.	0.43	0.03	*	.	.	0.22	0.17
Leu	152	.	A	B	.	.	.	.	0.13	0.43	*	.	.	-0.34	0.18
Leu	153	.	A	B	.	.	.	.	-0.28	0.81	*	.	.	-0.60	0.34
Cys	154	.	A	B	.	.	.	.	-0.62	0.51	.	*	.	-0.60	0.26
Gln	155	.	A	.	.	T	.	.	-0.02	0.54	*	.	F	-0.05	0.31
Ser	156	.	.	.	.	T	T	.	-0.72	0.77	*	.	F	0.35	0.40
Ser	157	.	.	.	.	T	T	.	-0.12	0.87	*	.	F	0.35	0.64
Gly	158	.	.	.	.	T	T	.	0.80	0.73	*	.	F	0.35	0.57
Trp	159	.	.	.	.	T	T	.	1.26	0.33	*	.	F	0.65	0.84

Phe	160	.	.	.	.	.	T	C	0.94	0.37	*	.	F	0.45	0.97
Pro	161	.	.	.	.	.	T	C	0.66	0.47	*	*	F	0.30	1.41
Arg	162	.	.	.	.	.	T	C	1.00	0.54	*	*	F	0.30	1.36
Pro	163	.	.	.	.	T	T	.	1.06	-0.37	*	*	F	1.40	3.13
Thr	164	.	.	.	.	T	.	.	1.39	-0.24	*	*	F	1.20	2.13
Ala	165	.	.	.	.	T	.	.	1.74	-0.67	*	*	F	1.50	2.17
Lys	166	.	.	.	.	T	.	.	1.74	-0.24	.	*	F	1.20	1.39
Trp	167	.	.	.	.	T	.	.	1.63	-0.24	.	*	F	1.54	1.49
Lys	168	.	.	.	.	.	.	C	1.50	-0.33	.	*	F	1.68	2.55
Gly	169	.	.	.	.	.	.	C	1.81	-0.40	.	*	F	2.02	1.26
Pro	170	.	.	.	.	.	T	C	2.40	0.00	.	*	F	1.96	2.08
Gln	171	.	.	.	.	T	T	.	1.54	-0.91	.	.	F	3.40	1.74
Gly	172	.	.	.	.	.	T	C	1.53	-0.23	.	.	F	2.56	1.45
Gln	173	.	.	B	.	.	T	.	1.18	-0.27	.	.	F	2.02	1.26
Asp	174	.	.	B	.	.	.	.	1.52	-0.21	.	.	F	1.82	1.05
Leu	175	.	.	B	.	.	.	.	1.43	-0.61	*	*	F	2.12	1.77
Ser	176	.	.	B	.	.	T	.	1.54	-0.66	*	*	F	2.32	1.37
Thr	177	.	.	B	.	.	T	.	1.58	-1.06	*	*	F	2.66	1.60
Asp	178	.	.	.	.	T	T	.	1.58	-0.57	*	.	F	3.40	2.80
Ser	179	.	.	.	.	.	T	C	1.69	-0.86	*	*	F	2.86	3.37
Arg	180	.	.	.	.	T	T	.	2.50	-1.24	*	*	F	3.06	4.57
Thr	181	.	.	.	.	T	T	.	2.20	-1.73	*	.	F	3.06	4.57
Asn	182	.	.	.	.	T	T	.	2.48	-1.11	*	.	F	3.06	3.37
Arg	183	.	.	B	.	.	T	.	2.13	-1.00	*	.	F	2.66	2.34
Asp	184	.	.	.	.	T	T	.	1.62	-0.57	*	.	F	3.40	1.61
Met	185	.	.	B	.	.	T	.	0.81	-0.37	*	.	.	2.06	0.82
His	186	.	.	B	.	.	T	.	1.12	0.01	*	.	.	1.12	0.36
Gly	187	.	.	B	.	.	T	.	0.27	0.01	*	*	.	0.78	0.36
Leu	188	.	.	B	B	.	.	.	0.16	0.66	*	*	.	-0.26	0.27
Phe	189	A	.	.	B	.	.	.	-0.73	0.04	.	*	.	-0.30	0.35
Asp	190	A	.	.	B	.	.	.	-0.43	0.23	.	*	.	-0.30	0.25
Val	191	A	.	.	B	.	.	.	-1.21	0.19	.	*	.	-0.30	0.40
Glu	192	A	.	.	B	.	.	.	-1.18	0.19	.	*	.	-0.30	0.38
Ile	193	A	.	.	B	.	.	.	-1.22	-0.11	.	*	.	0.30	0.33
Ser	194	A	.	.	B	.	.	.	-0.52	0.53	.	*	.	-0.60	0.33
Leu	195	A	A	.	B	.	.	.	-0.52	0.29	.	*	.	-0.30	0.33
Thr	196	A	A	.	B	.	.	.	0.33	0.29	.	*	.	-0.30	0.81
Val	197	A	A	.	B	.	.	.	-0.26	0.00	.	*	.	0.55	0.98
Gln	198	A	A	.	B	.	.	.	0.29	0.11	.	*	F	0.50	1.20
Glu	199	A	A	.	B	.	.	.	0.29	-0.14	.	.	F	1.20	0.82
Asn	200	.	.	.	.	T	T	.	0.21	-0.24	.	.	F	2.40	1.48
Ala	201	.	.	.	.	T	T	.	0.22	-0.20	.	.	F	2.50	0.60
Gly	202	.	.	.	.	T	T	.	0.41	-0.21	.	.	F	2.25	0.46
Ser	203	.	.	.	.	T	T	.	0.11	0.36	.	.	F	1.40	0.15
Ile	204	A	.	.	.	.	.	.	-0.49	0.34	*	*	.	0.40	0.21
Ser	205	A	.	.	.	.	.	.	-0.38	0.46	*	*	.	-0.15	0.21
Cys	206	.	.	B	.	.	.	.	0.18	0.03	*	*	.	-0.10	0.30
Ser	207	.	A	B	.	.	.	.	-0.07	0.14	*	*	.	-0.30	0.58
Met	208	A	A	.	.	.	.	.	0.20	-0.04	*	*	.	0.30	0.44
Arg	209	A	A	.	.	.	.	.	0.28	0.07	*	*	.	-0.15	1.11
His	210	A	A	.	.	.	.	.	0.28	0.19	.	.	.	-0.30	0.69
Ala	211	A	A	.	.	.	.	.	1.06	0.19	.	.	.	-0.30	0.93
His	212	A	A	.	.	.	.	.	1.36	-0.43	*	.	.	0.30	0.93
Leu	213	A	A	.	.	.	.	.	1.10	-0.43	*	.	.	0.45	1.18
Ser	214	A	A	.	.	.	.	.	0.99	-0.29	*	.	.	0.30	0.87
Arg	215	A	A	.	.	.	.	.	0.72	-0.79	*	*	F	0.90	1.10
Glu	216	A	A	.	.	.	.	.	1.42	-0.90	*	*	F	0.90	1.79
Val	217	A	.	.	B	.	.	.	0.60	-1.59	*	*	F	0.90	2.62
Glu	218	A	.	.	B	.	.	.	1.41	-1.33	*	*	F	0.75	0.99
Ser	219	A	.	.	B	.	.	.	0.82	-0.93	*	*	F	0.75	0.99
Arg	220	.	.	B	B	.	.	.	0.37	-0.24	*	*	F	0.45	0.94
Val	221	.	.	B	B	.	.	.	0.37	-0.46	.	*	F	0.45	0.54
Gln	222	.	.	B	B	.	.	.	0.91	-0.46	.	*	.	0.30	0.67
Ile	223	.	.	B	B	.	.	.	0.21	-0.36	.	*	.	0.30	0.49
Gly	224	.	.	B	B	.	.	.	-0.19	0.43	.	*	F	-0.45	0.57
Asp	225	.	.	.	B	.	.	C	-0.30	0.57	.	*	F	-0.25	0.29
Thr	226	.	.	B	B	.	.	.	0.34	0.17	*	.	.	-0.30	0.71
Phe	227	.	.	B	B	.	.	.	-0.54	-0.09	*	.	.	0.45	1.11
Phe	228	.	.	B	B	.	.	.	0.04	0.17	*	.	.	-0.30	0.47
Glu	229	.	.	B	B	.	.	.	0.10	0.56	*	.	.	-0.60	0.43
Pro	230	A	.	.	B	.	.	.	0.07	0.99	*	.	.	-0.60	0.53
Ile	231	A	.	.	B	.	.	.	-0.43	0.70	*	.	.	-0.60	0.83
Ser	232	A	A	.	B	.	.	.	-0.32	0.60	*	.	.	-0.60	0.39

Trp	233	A	A	.	B	.	.	.	0.07	1.10	.	.	.	-0.60	0.26
His	234	A	A	.	B	.	.	.	0.11	1.16	.	*	.	-0.60	0.53
Leu	235	A	A	.	B	.	.	.	-0.53	0.47	*	*	.	-0.60	0.79
Ala	236	A	A	.	B	.	.	.	-0.46	0.73	.	*	.	-0.60	0.56
Thr	237	A	A	.	B	.	.	.	-0.50	0.50	*	.	.	-0.60	0.34
Lys	238	.	A	B	B	.	.	.	-1.10	0.43	*	.	.	-0.60	0.40
Val	239	.	A	B	B	.	.	.	-1.88	0.43	*	.	.	-0.60	0.28
Leu	240	.	A	B	B	.	.	.	-1.73	0.61	*	.	.	-0.60	0.16
Gly	241	.	A	B	B	.	.	.	-1.81	0.70	*	.	.	-0.60	0.04
Ile	242	.	A	B	B	.	.	.	-1.84	1.27	*	.	.	-0.60	0.03
Leu	243	.	A	B	B	.	.	.	-2.70	1.06	*	.	.	-0.60	0.04
Cys	244	.	.	B	.	.	T	.	-2.54	1.06	.	.	.	-0.20	0.03
Cys	245	.	.	B	.	.	T	.	-2.43	1.41	.	.	.	-0.20	0.04
Gly	246	.	.	B	.	.	T	.	-2.43	1.51	.	.	.	-0.20	0.04
Leu	247	.	.	B	.	.	T	.	-2.43	1.26	.	.	.	-0.20	0.07
Phe	248	.	.	B	B	.	.	.	-2.48	1.37	.	.	.	-0.60	0.10
Phe	249	.	.	B	B	.	.	.	-2.16	1.44	.	.	.	-0.60	0.07
Gly	250	.	.	B	B	.	.	.	-2.30	1.44	.	.	.	-0.60	0.09
Ile	251	.	.	B	B	.	.	.	-1.91	1.44	.	.	.	-0.60	0.08
Val	252	A	A	.	B	.	.	.	-1.99	0.66	.	.	.	-0.60	0.19
Gly	253	A	A	.	B	.	.	.	-1.99	0.56	.	.	.	-0.60	0.14
Leu	254	A	A	.	B	.	.	.	-1.99	0.91	.	.	.	-0.60	0.17
Lys	255	.	A	B	B	.	.	.	-1.94	1.01	.	.	.	-0.60	0.20
Ile	256	.	A	B	B	.	.	.	-1.01	0.76	*	.	.	-0.60	0.27
Phe	257	.	A	B	B	.	.	.	-0.86	0.33	*	*	.	-0.30	0.65
Phe	258	A	A	.	B	.	.	.	-0.51	0.43	*	*	.	-0.60	0.28
Ser	259	A	A	.	B	.	.	.	0.01	0.83	.	*	.	-0.60	0.69
Lys	260	A	A	.	B	.	.	.	0.01	1.06	.	*	.	-0.60	0.84
Phe	261	A	A	.	B	.	.	.	0.01	0.27	.	*	.	-0.15	1.94
Gln	262	A	A	.	B	.	.	.	0.71	0.17	*	*	.	-0.15	1.01
Trp	263	A	A	.	B	.	.	.	0.82	0.19	*	*	.	-0.30	0.88
Lys	264	A	A	.	B	.	.	.	1.12	0.69	*	*	.	-0.45	1.02
Ile	265	A	A	.	B	.	.	.	0.27	-0.10	*	*	.	0.45	1.02
Gln	266	A	A	.	B	.	.	.	0.97	0.19	.	*	.	-0.30	0.80
Ala	267	A	A	.	B	.	.	.	0.68	-0.73	.	*	.	0.60	0.67
Glu	268	A	A	.	B	.	.	.	1.08	0.19	.	*	.	-0.15	1.01
Leu	269	A	A	.	.	.	.	.	1.14	-0.50	.	*	.	0.75	1.14
Asp	270	A	A	.	.	.	.	.	2.08	-0.90	.	*	.	0.75	2.21
Trp	271	A	A	.	.	.	.	.	2.04	-1.40	.	*	.	1.05	2.55
Arg	272	A	A	.	.	.	.	.	2.29	-0.90	.	*	.	1.35	4.20
Arg	273	A	.	.	.	.	T	.	2.29	-1.16	.	*	F	2.20	2.49
Lys	274	A	.	.	.	.	T	.	2.51	-0.76	.	*	F	2.50	4.10
His	275	.	.	.	.	.	T	C	2.51	-1.17	.	*	F	3.00	2.12
Gly	276	.	.	.	.	.	T	C	1.99	-1.17	.	*	F	2.70	1.87
Gln	277	.	A	.	.	.	.	C	1.99	-0.49	.	*	F	1.55	0.77
Ala	278	A	A	.	.	.	.	.	1.88	-0.49	*	*	F	1.20	1.11
Glu	279	A	A	.	.	.	.	.	1.24	-0.99	*	.	.	1.05	1.87
Leu	280	A	A	.	.	.	.	.	1.39	-0.91	*	*	F	0.90	1.09
Arg	281	A	A	.	.	.	.	.	1.78	-1.31	*	*	F	0.90	2.12
Asp	282	A	A	.	.	.	.	.	1.74	-1.81	*	*	F	0.90	2.45
Ala	283	A	A	.	.	.	.	.	1.74	-1.31	*	.	F	0.90	4.04
Arg	284	A	A	.	.	.	.	.	0.89	-1.50	*	.	F	0.90	2.08
Lys	285	A	A	.	.	.	.	.	1.70	-0.86	*	.	F	0.75	0.93
His	286	A	A	.	.	.	.	.	0.73	-0.86	*	.	.	0.75	1.59
Ala	287	A	A	.	.	.	.	.	0.42	-0.71	.	*	.	0.60	0.60
Val	288	.	A	B	.	.	.	.	0.20	-0.23	.	*	.	0.30	0.43
Glu	289	.	A	B	.	.	.	.	0.09	0.46	.	*	.	-0.60	0.26
Val	290	.	A	B	.	.	.	.	-0.17	-0.04	.	*	.	0.30	0.43
Thr	291	A	A	.	.	.	.	.	-0.13	-0.11	.	*	.	0.30	0.91
Leu	292	A	A	.	.	.	.	.	0.14	-0.76	.	*	F	0.75	0.91
Asp	293	A	.	.	.	.	T	.	0.41	-0.27	.	*	F	1.00	1.76
Pro	294	A	.	.	.	.	T	.	0.38	-0.41	.	*	F	1.00	1.23
Glu	295	A	.	.	.	.	T	.	1.02	-0.40	.	*	F	1.00	2.03
Thr	296	A	.	.	.	.	T	.	1.38	-0.66	.	.	F	1.30	1.88
Ala	297	A	A	.	.	.	.	.	1.38	-0.66	.	.	F	0.90	2.44
His	298	A	A	.	.	.	.	.	0.71	-0.40	.	*	F	0.60	1.16
Pro	299	A	A	.	.	.	.	.	0.07	0.17	.	*	F	-0.15	0.43
Lys	300	A	A	.	B	.	.	.	-0.23	0.33	.	.	F	-0.15	0.32
Leu	301	A	A	.	B	.	.	.	0.08	0.21	.	*	.	-0.30	0.31
Cys	302	.	A	B	B	.	.	.	-0.14	-0.29	.	*	.	0.30	0.34
Val	303	A	A	.	B	.	.	.	-0.07	-0.03	.	.	.	0.30	0.14
Ser	304	A	A	.	.	.	.	.	-0.17	-0.03	*	.	F	0.45	0.34
Asp	305	A	.	.	.	.	.	.	-1.07	-0.23	*	.	F	0.65	0.91

Leu	306	A	.	.	B	.	.	.	-0.57	-0.16	*	.	F	0.45	0.91
Lys	307	A	.	.	B	.	.	.	0.07	-0.31	*	.	F	0.45	0.98
Thr	308	A	.	.	B	.	.	.	1.03	-0.20	*	.	F	0.45	0.80
Val	309	A	.	.	B	.	.	.	1.38	-0.20	*	.	F	0.60	1.89
Thr	310	.	A	B	B	.	.	.	0.79	-0.89	.	.	.	0.75	1.89
His	311	.	A	B	B	.	.	.	1.39	-0.39	.	.	F	0.60	1.32
Arg	312	.	A	.	B	T	.	.	1.34	-0.44	.	.	F	1.00	2.75
Lys	313	.	A	.	B	.	.	C	1.66	-0.69	*	.	F	1.10	3.31
Ala	314	.	A	.	.	.	.	C	1.66	-1.17	*	.	F	1.10	4.21
Pro	315	.	A	.	.	.	.	C	1.76	-1.03	*	.	F	1.10	1.59
Gln	316	A	A	.	.	.	.	.	1.76	-0.60	*	.	F	0.90	1.23
Glu	317	A	A	.	.	.	.	.	1.34	-0.10	*	.	F	0.60	1.66
Val	318	.	.	B	.	.	T	.	1.30	-0.21	*	.	F	1.00	1.44
Pro	319	A	.	.	.	.	T	.	1.93	-0.64	*	.	F	1.30	1.44
His	320	A	.	.	.	.	T	.	2.26	-1.04	*	.	F	1.30	1.66
Ser	321	A	.	.	.	.	T	.	1.56	-1.04	*	.	F	1.30	4.38
Glu	322	A	A	.	.	.	.	.	1.24	-0.90	*	.	F	0.90	2.46
Lys	323	A	A	.	B	.	.	.	2.21	-0.84	*	.	F	0.90	2.60
Arg	324	A	A	.	B	.	.	.	2.47	-1.34	*	.	F	0.90	3.81
Phe	325	A	A	.	B	.	.	.	2.20	-1.73	*	.	F	0.90	4.40
Thr	326	A	A	.	B	.	.	.	1.64	-1.34	*	.	F	0.90	2.95
Arg	327	A	.	.	B	.	.	.	0.79	-0.70	*	.	F	0.90	1.12
Lys	328	.	.	B	B	.	.	.	0.16	-0.06	*	.	F	0.45	0.96
Ser	329	.	.	B	B	.	.	.	-0.26	-0.34	*	.	F	0.45	0.67
Val	330	.	.	B	B	.	.	.	0.44	-0.44	*	.	.	0.30	0.46
Val	331	.	.	B	B	.	.	.	0.46	-0.04	*	.	.	0.30	0.40
Ala	332	.	.	B	B	.	.	.	-0.36	0.34	*	.	.	-0.30	0.40
Ser	333	.	.	B	.	.	T	.	-0.40	0.74	.	.	F	-0.05	0.46
Gln	334	A	.	.	.	.	T	.	-0.69	0.50	.	.	F	0.10	1.08
Ser	335	A	.	.	.	.	T	.	-0.18	0.36	.	.	F	0.40	1.08
Phe	336	A	.	.	.	.	T	.	0.72	0.29	*	.	F	0.25	0.80
Gln	337	A	.	.	.	.	.	.	1.28	-0.10	*	.	.	0.50	0.92
Ala	338	.	.	.	.	.	.	C	1.33	0.00	*	.	.	0.10	0.94
Gly	339	.	.	.	.	.	T	C	1.04	0.37	*	.	.	0.45	1.69
Lys	340	.	.	.	.	.	T	C	1.34	0.50	*	.	.	0.15	1.03
His	341	.	.	.	.	.	T	C	1.19	0.10	*	*	.	0.45	1.76
Tyr	342	.	.	B	.	.	T	.	1.19	0.24	*	*	.	0.25	1.32
Trp	343	.	.	B	.	.	.	.	1.43	-0.19	.	*	.	0.65	1.10
Glu	344	.	.	B	.	.	.	.	1.43	0.24	.	*	.	0.24	0.80
Val	345	.	.	B	.	.	T	.	1.36	0.17	.	*	.	0.78	0.51
Asp	346	.	.	.	.	T	T	.	1.39	-0.09	.	.	F	2.27	0.66
Gly	347	.	.	.	.	T	T	.	1.68	-0.60	.	*	F	2.91	0.61
Gly	348	.	.	.	.	T	T	.	2.08	-0.60	.	*	F	3.40	1.64
His	349	.	.	.	.	.	.	C	1.79	-1.24	*	*	F	2.66	1.92
Asn	350	.	.	.	.	.	T	C	2.76	-0.33	.	*	F	2.22	2.04
Lys	351	.	.	.	.	T	T	.	1.90	-0.76	.	*	F	2.38	4.05
Arg	352	.	.	.	.	T	T	.	1.90	-0.54	.	*	.	1.89	2.21
Trp	353	.	.	.	.	T	T	.	1.39	-0.61	.	*	.	1.55	1.36
Arg	354	.	.	B	B	.	.	.	0.76	-0.37	*	*	.	0.30	0.50
Val	355	.	.	B	B	.	.	.	0.87	0.20	*	*	.	-0.30	0.14
Gly	356	.	.	B	B	.	.	.	0.82	0.20	*	*	.	-0.30	0.26
Val	357	.	.	B	B	.	.	.	0.71	-0.71	.	*	.	0.60	0.22
Cys	358	.	.	B	.	.	T	.	0.14	-0.71	.	*	.	1.00	0.49
Arg	359	.	.	B	.	.	T	.	0.03	-0.71	*	.	.	1.00	0.37
Asp	360	.	.	B	.	.	T	.	1.00	-1.14	.	.	F	1.15	0.83
Asp	361	A	.	.	.	.	T	.	1.46	-1.79	.	.	F	1.30	3.04
Val	362	A	.	.	.	.	.	.	2.36	-2.36	.	.	F	1.10	3.04
Asp	363	A	.	.	.	.	T	.	3.02	-2.36	.	*	F	1.30	3.64
Arg	364	A	.	.	.	.	T	.	2.67	-2.36	.	*	F	1.30	3.78
Arg	365	A	.	.	.	.	T	.	1.81	-1.60	*	.	F	1.30	7.97
Lys	366	.	.	B	.	.	T	.	1.50	-1.60	.	.	F	1.30	3.54
Glu	367	.	.	B	B	.	.	.	1.54	-1.11	.	.	F	0.90	2.61
Tyr	368	.	.	B	B	.	.	.	1.24	-0.43	.	.	.	0.45	1.10
Val	369	.	.	B	B	.	.	.	0.92	-0.04	.	.	.	0.55	0.74
Thr	370	.	.	B	B	.	.	.	0.81	0.39	.	.	.	0.20	0.66
Leu	371	.	.	B	B	.	.	.	0.73	0.39	.	.	.	0.45	0.70
Ser	372	.	.	B	.	.	T	.	0.39	0.13	.	.	F	1.40	1.28
Pro	373	.	.	.	.	T	T	.	0.39	-0.09	.	.	F	2.50	0.88
Asp	374	.	.	.	.	T	T	.	0.96	0.19	.	.	F	1.80	1.67
His	375	.	.	.	.	T	T	.	0.41	0.41	.	.	.	1.10	1.31
Gly	376	.	.	.	B	T	.	.	0.41	0.67	*	*	.	0.30	0.63
Tyr	377	.	.	B	B	.	.	.	0.82	0.93	*	*	.	-0.35	0.31
Trp	378	.	.	B	B	.	.	.	0.22	0.93	*	*	.	-0.60	0.45

Val	379	.	.	B	B	.	.	.	0.22	1.11	*	*	.	-0.60	0.37
Leu	380	.	.	B	B	.	.	.	-0.09	1.09	*	*	.	-0.60	0.38
Arg	381	.	.	B	B	.	.	.	0.26	0.76	*	*	.	-0.60	0.36
Leu	382	.	.	B	B	.	.	.	0.47	-0.16	*	*	.	0.30	0.84
Asn	383	.	.	.	B	.	.	C	-0.06	-0.30	*	*	F	0.80	1.39
Gly	384	.	.	.	.	.	.	C	0.56	-0.30	*	*	F	0.85	0.58
Glu	385	.	.	.	.	.	.	C	0.67	0.46	.	*	F	0.10	1.11
His	386	.	.	B	B	.	.	.	0.24	0.56	.	*	.	-0.60	0.60
Leu	387	.	.	B	B	.	.	.	0.24	0.64	.	*	.	-0.60	0.87
Tyr	388	.	.	B	B	.	.	.	0.24	0.90	.	.	.	-0.60	0.42
Phe	389	.	.	B	B	.	.	.	0.38	1.30	.	*	.	-0.60	0.49
Thr	390	.	.	B	B	.	.	.	0.49	1.23	.	*	.	-0.60	0.92
Leu	391	.	.	B	B	.	.	.	-0.18	0.54	*	*	.	-0.45	1.15
Asn	392	.	.	.	.	.	T	C	-0.26	0.57	*	*	.	0.15	1.15
Pro	393	.	.	.	.	T	T	.	-0.31	0.47	*	*	.	0.20	0.56
Arg	394	.	.	.	.	T	T	.	-0.47	0.37	*	*	.	0.50	0.91
Phe	395	.	.	B	.	.	T	.	-0.86	0.33	*	*	.	0.10	0.42
Ile	396	.	.	B	B	.	.	.	-0.26	0.71	*	*	.	-0.60	0.23
Ser	397	.	.	B	B	.	.	.	-0.14	0.71	*	.	.	-0.60	0.19
Val	398	.	.	B	B	.	.	.	-0.24	0.71	*	.	.	-0.60	0.42
Phe	399	.	.	B	B	.	.	.	-0.57	0.41	*	.	.	-0.60	0.86
Pro	400	.	.	.	.	T	.	.	-0.08	0.16	*	.	F	0.73	1.00
Arg	401	.	.	.	.	T	.	.	0.50	0.20	*	.	F	1.16	2.07
Thr	402	.	.	.	.	.	.	C	0.84	0.04	*	.	F	1.24	3.46
Pro	403	.	.	.	.	.	T	C	0.81	-0.74	.	.	F	2.62	4.47
Pro	404	.	.	.	.	T	T	.	1.17	-0.49	*	.	F	2.80	1.60
Thr	405	.	.	.	.	T	T	.	0.52	-0.06	*	.	F	2.52	1.10
Lys	406	.	.	B	.	.	T	.	-0.29	0.10	*	.	F	1.09	0.53
Ile	407	.	.	B	B	.	.	.	-0.79	0.46	*	*	.	-0.04	0.29
Gly	408	.	.	B	B	.	.	.	-0.58	0.71	.	*	.	-0.32	0.17
Val	409	.	.	B	B	.	.	.	-0.61	0.23	.	*	.	-0.30	0.14
Phe	410	.	.	B	B	.	.	.	-0.30	0.99	.	*	.	-0.60	0.31
Leu	411	.	.	B	B	.	.	.	-1.01	0.30	.	*	.	-0.08	0.55
Asp	412	.	.	B	.	.	T	.	-0.47	0.44	.	.	.	0.24	0.40
Tyr	413	.	.	B	.	.	T	.	-0.43	0.23	.	.	.	0.76	0.45
Glu	414	.	.	.	.	T	T	.	-0.47	-0.07	.	.	.	1.98	0.80
Cys	415	.	.	.	.	T	T	.	-0.07	-0.07	.	.	.	2.20	0.33
Gly	416	.	.	.	B	T	.	.	0.04	0.31	.	.	.	0.98	0.29
Thr	417	.	.	B	B	.	.	.	-0.66	0.34	.	.	.	0.36	0.14
Ile	418	.	.	B	B	.	.	.	-0.41	1.13	.	.	.	-0.16	0.23
Ser	419	.	.	B	B	.	.	.	-1.30	0.96	.	.	.	-0.38	0.37
Phe	420	.	.	B	B	.	.	.	-0.63	1.21	.	.	.	-0.60	0.18
Phe	421	.	.	B	B	.	.	.	-0.29	1.13	.	.	.	-0.60	0.42
Asn	422	.	.	B	B	.	.	.	0.02	0.44	.	.	.	-0.47	0.52
Ile	423	.	.	.	B	.	.	C	0.61	0.46	.	.	.	0.01	1.04
Asn	424	.	.	.	B	.	.	C	0.10	0.06	.	.	F	0.59	1.61
Asp	425	.	.	.	.	T	T	.	-0.09	-0.04	.	.	F	1.77	0.83
Gln	426	.	.	.	.	T	T	.	0.37	0.24	.	*	F	1.30	0.83
Ser	427	.	.	.	.	T	T	.	0.06	0.31	.	.	F	1.17	0.80
Leu	428	.	.	B	.	.	T	.	0.13	0.40	.	.	.	0.49	0.70
Ile	429	.	.	B	B	.	.	.	-0.18	1.09	.	.	.	-0.34	0.33
Tyr	430	.	.	B	B	.	.	.	-0.84	1.17	.	*	.	-0.47	0.36
Thr	431	.	.	B	B	.	.	.	-0.73	1.36	*	*	.	-0.60	0.23
Leu	432	.	.	B	B	.	.	.	-1.13	0.67	*	*	.	-0.60	0.65
Thr	433	.	.	B	B	.	.	.	-0.32	0.77	*	*	.	-0.60	0.36
Cys	434	.	A	B	B	.	.	.	0.22	0.01	*	*	.	-0.30	0.43
Arg	435	.	A	B	B	.	.	.	-0.34	-0.04	*	*	.	0.30	0.52
Phe	436	.	A	B	B	.	.	.	-0.84	-0.04	*	*	.	0.30	0.29
Glu	437	.	A	B	B	.	.	.	0.08	0.16	*	*	.	-0.30	0.45
Gly	438	.	A	.	.	T	.	.	0.18	-0.41	*	*	.	0.70	0.45
Leu	439	.	A	.	.	T	.	.	0.60	0.01	*	*	.	0.10	0.81
Leu	440	.	A	.	B	.	.	C	-0.40	-0.01	*	*	F	0.65	0.73
Arg	441	.	A	.	B	.	.	C	0.30	0.67	*	*	.	-0.40	0.52
Pro	442	.	.	B	B	.	.	.	0.06	0.24	*	*	.	-0.15	1.09
Tyr	443	.	.	B	B	.	.	.	0.19	0.31	*	*	.	-0.15	2.07
Ile	444	.	.	B	B	.	.	.	0.70	0.06	*	*	.	-0.15	1.63
Glu	445	.	.	B	B	.	.	.	1.27	0.44	*	*	.	-0.45	1.42
Tyr	446	.	.	B	.	.	T	.	1.16	0.77	.	*	.	-0.05	1.42
Pro	447	.	.	B	.	.	T	.	1.37	0.41	.	.	F	0.10	3.25
Ser	448	.	.	.	.	T	T	.	1.61	-0.27	.	.	F	1.40	3.25
Tyr	449	.	.	.	.	T	T	.	2.50	0.13	.	.	F	0.80	3.59
Asn	450	.	.	.	.	T	.	.	2.16	-0.23	.	.	F	1.50	3.73
Glu	451	.	.	.	.	T	T	.	2.09	-0.23	.	.	F	2.00	2.76

Gln	452	.	.	.	.	T	T	.	2.09	-0.13	.	.	F	2.30	2.54
Asn	453	.	.	.	.	T	T	.	2.50	-0.46	.	.	F	2.60	2.44
Gly	454	.	.	.	.	.	T	C	2.74	-0.86	.	*	F	3.00	2.76
Thr	455	.	.	.	.	.	T	C	2.79	-0.86	.	.	F	2.70	2.66
Pro	456	.	.	.	.	.	T	C	2.79	-1.26	.	*	F	2.40	3.31
Arg	457	.	.	.	.	T	T	.	2.79	-1.26	.	*	F	2.30	5.80
Asp	458	.	.	.	.	T	T	.	2.40	-1.29	.	*	F	2.00	6.95
Lys	459	.	.	B	.	.	.	.	2.36	-1.34	.	.	.	0.95	5.75
Gln	460	.	.	B	.	.	.	.	2.28	-1.34	.	.	.	0.95	3.75
Gln	461	.	.	B	.	.	.	.	2.10	-0.91	.	.	.	0.95	2.87

TABLE 10

cDNA Plasmid:V	Library Code
HE8NC81	H0012 H0013 H0056 H0059 H0063 H0083 H0098 H0144 H0156 H0163 H0170 H0177 H0181 H0321 H0327 H0333 H0345 H0392 H0412 H0427 H0436 H0457 H0494 H0520 H0521 H0539 H0542 H0550 H0551 H0556 H0586 H0616 H0619 H0646 H0656 H0658 H0660 H0662 H0663 H0670 H0672 H0684 L1290 S0015 S0026 S0037 S0132 S0206 S0278 S0358 S0360 S0374 S0452 S3014
HDPPA04	H0004 H0494 H0521 H0522 H0591 H0641 L1290 S0452 T0049
HTTDB46	H0036 H0040 S0360
HCECR39	H0052 H0090 H0486 H0556 H0580 L1290 S0046 S0270
HCE2X64	H0009 H0052 H0144 H0194 H0569 L1290 S0001 S0049 S0222 S0388 S6024 S6028 T0006 T0010
HEMFH17	H0052 H0090 H0486 H0580 L1290 S0046 S0270 S0386
HSIDS22	H0002 H0013 H0020 H0030 H0036 H0040 H0046 H0051 H0052 H0059 H0156 H0316 H0412 H0423 H0521 H0529 H0545 H0547 H0555 H0556 H0575 H0590 H0617 H0622 H0631 H0632 H0641 H0644 H0656 H0657 H0659 H0660 H0662 H0665 H0666 H0690 H0708 H0716 L1290 S0003 S0045 S0126 S0194 S0214 S0218 S0242 S0276 S0278 S0356 S0358 S0360 S0374 S0376 S0380 S0408 S0422 S0434 S0476 S3014 T0002

TABLE 11

SEQ ID NO: X	Cytologic Band or Chromosome:	OMIM ID:
2	Chromosome 1	
5	Chromosome 6	
6	Chromosome 1	

TABLE 12

Library Code	Library Description	Disease
H0002	Human Adult Heart	
H0004	Human Adult Spleen	
H0009	Human Fetal Brain	
H0012	Human Fetal Kidney	
H0013	Human 8 Week Whole Embryo	

H0020	Human Hippocampus	
H0030	Human Placenta	
H0036	Human Adult Small Intestine	
H0040	Human Testes Tumor	disease
H0046	Human Endometrial Tumor	disease
H0051	Human Hippocampus	
H0052	Human Cerebellum	
H0056	Human Umbilical Vein, Endo. remake	
H0059	Human Uterine Cancer	disease
H0063	Human Thymus	
H0083	HUMAN JURKAT MEMBRANE BOUND POLYSOMES	
H0090	Human T-Cell Lymphoma	disease
H0098	Human Adult Liver, subtracted	
H0144	Nine Week Old Early Stage Human	
H0156	Human Adrenal Gland Tumor	disease
H0163	Human Synovium	
H0170	12 Week Old Early Stage Human	
H0177	CAMA1Ee Cell Line	
H0181	Human Primary Breast Cancer	disease
H0194	Human Cerebellum, subtracted	
H0316	HUMAN STOMACH	
H0321	HUMAN SCHWANOMA	disease
H0327	human corpus colosum	
H0333	Hemangiopericytoma	disease
H0345	SKIN	
H0392	H. Meningima, M1	
H0412	Human umbilical vein endothelial cells, IL-4 induced	
H0423	T-Cell PHA 24 hrs	
H0427	Human Adipose	
H0436	Resting T-Cell Library,II	
H0457	Human Eosinophils	
H0486	Hodgkin's Lymphoma II	disease
H0494	Keratinocyte	
H0520	NTERA2 + retinoic acid, 14 days	
H0521	Primary Dendritic Cells, lib 1	
H0522	Primary Dendritic cells,frac 2	
H0529	Myoloid Progenitor Cell Line	
H0539	Pancreas Islet Cell Tumor	disease
H0542	T Cell helper I	
H0545	Human endometrial stromal cells-treated with progesterone	
H0547	NTERA2 teratocarcinoma cell line+retinoic acid (14 days)	
H0550	H. Epididiymus, cauda	

H0551	Human Thymus Stromal Cells	
H0555	Rejected Kidney, lib 4	disease
H0556	Activated T-cell(12h)/Thiouridine-re-excision	
H0569	Human Fetal Brain, normalized CO	
H0575	Human Adult Pulmonary,re-excision	
H0580	Dendritic cells, pooled	
H0586	Healing groin wound, 6.5 hours post incision	disease
H0590	Human adult small intestine,re-excision	
H0591	Human T-cell lymphoma,re-excision	disease
H0616	Human Testes, Reexcision	
H0617	Human Primary Breast Cancer Reexcision	disease
H0619	Fetal Heart	
H0622	Human Pancreas Tumor, Reexcision	disease
H0631	Saos2, Dexamethosome Treated	
H0632	Hepatocellular Tumor,re-excision	
H0641	LPS activated derived dendritic cells	
H0644	Human Placenta (re-excision)	
H0646	Lung, Cancer (4005313 A3): Invasive Poorly Differentiated Lung Adenocarcinoma,	
H0656	B-cells (unstimulated)	
H0657	B-cells (stimulated)	
H0658	Ovary, Cancer (9809C332): Poorly differentiated adenocarcinoma	disease
H0659	Ovary, Cancer (15395A1F): Grade II Papillary Carcinoma	disease
H0660	Ovary, Cancer: (15799A1F) Poorly differentiated carcinoma	disease
H0662	Breast, Normal: (4005522B2)	
H0663	Breast, Cancer: (4005522 A2)	disease
H0665	Stromal cells 3.88	
H0666	Ovary, Cancer: (4004332 A2)	disease
H0670	Ovary, Cancer(4004650 A3): Well-Differentiated Micropapillary Serous Carcinoma	
H0672	Ovary, Cancer: (4004576 A8)	
H0684	Ovarian cancer, Serous Papillary Adenocarcinoma	
H0690	Ovarian Cancer, # 9702G001	
H0708	Human Skeletal Muscle	
H0716	Adipose tissue (diabetic type II)#41689	
L1290	Soares_placenta_8to9weeks_2NbHP8to9W	
S0001	Brain frontal cortex	
S0003	Human Osteoclastoma	disease
S0015	Kidney medulla	
S0026	Stromal cell TF274	
S0037	Smooth muscle, IL1b induced	
S0045	Endothelial cells-control	

S0046	Endothelial-induced	
S0049	Human Brain, Striatum	
S0126	Osteoblasts	
S0132	Epithelial-TNFa and INF induced	
S0194	Synovial hypoxia	
S0206	Smooth Muscle- HASTE normalized	
S0214	Human Osteoclastoma, re-excision	disease
S0218	Apoptotic T-cell, re-excision	
S0222	H. Frontal cortex,epileptic,re-excision	disease
S0242	Synovial Fibroblasts (Il1/TNF), subt	
S0270	PTMIX	
S0276	Synovial hypoxia-RSF subtracted	
S0278	H Macrophage (GM-CSF treated), re-excision	
S0356	Colon Carcinoma	disease
S0358	Colon Normal III	
S0360	Colon Tumor II	disease
S0374	Normal colon	
S0376	Colon Tumor	disease
S0380	Pancreas Tumor PCA4 Tu	disease
S0386	Human Whole Brain, re-excision	
S0388	Human Hypothalamus,schizophrenia, re-excision	disease
S0408	Colon, normal	
S0422	Mo7e Cell Line GM-CSF treated (1ng/ml)	
S0434	Stomach Normal	disease
S0452	Thymus	
S0476	Epithelial-TNFa and INF induced	
S3014	Smooth muscle, serum induced,re-exc	
S6024	Alzheimers, spongy change	disease
S6028	Human Manic Depression Tissue	disease
T0002	Activated T-cells	
T0006	Human Pineal Gland	
T0010	Human Infant Brain	
T0049	Aorta endothelial cells + TNF-a	

[961] Having generally described the invention, the same will be more readily understood by reference to the following examples, which are provided by way of illustration and are not intended as limiting.

EXAMPLES

Example 1: Isolation of a Selected cDNA Clone From the Deposited Sample

[962] Each cDNA clone in a cited ATCC deposit is contained in a plasmid vector. Table 1 identifies the vectors used to construct the cDNA library from which each clone was isolated. In many cases, the vector used to construct the library is a phage vector from which a plasmid has been excised. The table immediately below correlates the related plasmid for each phage vector used in constructing the cDNA library. For example, where a particular clone is identified in Table 1 as being isolated in the vector "Lambda Zap," the corresponding deposited clone is in "pBluescript."

Vector Used to Construct Library	Corresponding Deposited Plasmid
Lambda Zap	pBluescript (pBS)
Uni-Zap XR	pBluescript (pBS)
Zap Express	pBK
lafmid BA	plafmid BA
pSport1	pSport1
pCMVSport 2.0	pCMVSport 2.0
pCMVSport 3.0	pCMVSport 3.0
pCR®2.1	pCR®2.1

[963] Vectors Lambda Zap (U.S. Patent Nos. 5,128,256 and 5,286,636), Uni-Zap XR (U.S. Patent Nos. 5,128, 256 and 5,286,636), Zap Express (U.S. Patent Nos. 5,128,256 and 5,286,636), pBluescript (pBS) (Short et al., *Nucleic Acids Res.*, 16:7583-7600 (1988); Alting-Mees et al., *Nucleic Acids Res.*, 17:9494 (1989)) and pBK (Alting-Mees et al., *Strategies*, 5:58-61 (1992)) are commercially available from Stratagéne Cloning Systems, Inc., 11011 N. Torrey Pines Road, La Jolla, CA, 92037. pBS contains an ampicillin resistance gene and pBK contains a neomycin resistance gene. Both can be transformed into E. coli strain XL-1 Blue, also available from Stratagene. pBS comes in 4 forms SK+, SK-, KS+ and KS. The S and K refers to the orientation of the polylinker to the T7 and T3 primer sequences which flank the polylinker region ("S" is for SacI and "K" is for KpnI which are the first sites on each respective end of the linker). "+" or "-" refer to the orientation of the f1 origin of

replication ("ori"), such that in one orientation, single stranded rescue initiated from the fl ori generates sense strand DNA and in the other, antisense.

[964] Vectors pSport1, pCMVSport 2.0 and pCMVSport 3.0, were obtained from Life Technologies, Inc., P. O. Box 6009, Gaithersburg, MD 20897. All Sport vectors contain an ampicillin resistance gene and may be transformed into E. coli strain DH10B, also available from Life Technologies. (See, for instance; Gruber, C. E., et al., Focus 15:59 (1993)). Vector lafmid BA (Bento Soares, Columbia University, NY) contains an ampicillin resistance gene and can be transformed into E. coli strain XL-1 Blue. Vector pCR®2.1, which is available from Invitrogen, 1600 Faraday Avenue, Carlsbad, CA 92008, contains an ampicillin resistance gene and may be transformed into E. coli strain DH10B, available from Life Technologies. (See, for instance, Clark, *Nuc. Acids Res.*, 16:9677-9686 (1988) and Mead et al., *Bio/Technology*, 9 (1991)). Preferably, a polynucleotide of the present invention does not comprise the phage vector sequences identified for the particular clone in Table 1, as well as the corresponding plasmid vector sequences designated above.

[965] The deposited material in the sample assigned the ATCC Deposit Number cited in Table 1 for any given cDNA clone also may contain one or more additional plasmids, each comprising a cDNA clone different from that given clone. Thus, deposits sharing the same ATCC Deposit Number contain at least a plasmid for each cDNA Plasmid:V identified in Table 1. Typically, each ATCC deposit sample cited in Table 1 comprises a mixture of approximately equal amounts (by weight) of about 50 plasmid DNAs, each containing a different cDNA clone; but such a deposit sample may include plasmids for more or less than 50 cDNA clones, up to about 500 cDNA clones.

[966] Two approaches can be used to isolate a particular clone from the deposited sample of plasmid DNAs cited for that clone in Table 1. First, a plasmid is directly isolated by screening the clones using a polynucleotide probe corresponding to SEQ ID NO:X.

[967] Particularly, a specific polynucleotide with 30-40 nucleotides is synthesized using an Applied Biosystems DNA synthesizer according to the sequence reported. The oligonucleotide is labeled, for instance, with ^{32}P-γ-ATP using T4 polynucleotide kinase and purified according to routine methods. (E.g., Maniatis et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Press, Cold Spring, NY (1982)). The plasmid mixture is transformed into a suitable host, as indicated above (such as XL-1 Blue (Stratagene)) using techniques known to those of skill in the art, such as those provided by

the vector supplier or in related publications or patents cited above. The transformants are plated on 1.5% agar plates (containing the appropriate selection agent, e.g., ampicillin) to a density of about 150 transformants (colonies) per plate. These plates are screened using Nylon membranes according to routine methods for bacterial colony screening (e.g., Sambrook et al., Molecular Cloning: A Laboratory Manual, 2nd Edit., (1989), Cold Spring Harbor Laboratory Press, pages 1.93 to 1.104), or other techniques known to those of skill in the art.

[968] Alternatively, two primers of 17-20 nucleotides derived from both ends of the SEQ ID NO:X (i.e., within the region of SEQ ID NO:X bounded by the 5' NT and the 3' NT of the clone defined in Table 1) are synthesized and used to amplify the desired cDNA using the deposited cDNA plasmid as a template. The polymerase chain reaction is carried out under routine conditions, for instance, in 25 µl of reaction mixture with 0.5 ug of the above cDNA template. A convenient reaction mixture is 1.5-5 mM $MgCl_2$, 0.01% (w/v) gelatin, 20 µM each of dATP, dCTP, dGTP, dTTP, 25 pmol of each primer and 0.25 Unit of Taq polymerase. Thirty five cycles of PCR (denaturation at 94°C for 1 min; annealing at 55°C for 1 min; elongation at 72°C for 1 min) are performed with a Perkin-Elmer Cetus automated thermal cycler. The amplified product is analyzed by agarose gel electrophoresis and the DNA band with expected molecular weight is excised and purified. The PCR product is verified to be the selected sequence by subcloning and sequencing the DNA product.

[969] Several methods are available for the identification of the 5' or 3' non-coding portions of a gene which may not be present in the deposited clone. These methods include but are not limited to, filter probing, clone enrichment using specific probes, and protocols similar or identical to 5' and 3' "RACE" protocols which are well known in the art. For instance, a method similar to 5' RACE is available for generating the missing 5' end of a desired full-length transcript. (Fromont-Racine et al., *Nucleic Acids Res.*, 21(7):1683-1684 (1993)).

[970] Briefly, a specific RNA oligonucleotide is ligated to the 5' ends of a population of RNA presumably containing full-length gene RNA transcripts. A primer set containing a primer specific to the ligated RNA oligonucleotide and a primer specific to a known sequence of the gene of interest is used to PCR amplify the 5' portion of the desired full-length gene. This amplified product may then be sequenced and used to generate the full length gene.

[971] This above method starts with total RNA isolated from the desired source, although poly-A+ RNA can be used. The RNA preparation can then be treated with phosphatase if necessary to eliminate 5' phosphate groups on degraded or damaged RNA which may interfere with the later RNA ligase step. The phosphatase should then be inactivated and the RNA treated with tobacco acid pyrophosphatase in order to remove the cap structure present at the 5' ends of messenger RNAs. This reaction leaves a 5' phosphate group at the 5' end of the cap cleaved RNA which can then be ligated to an RNA oligonucleotide using T4 RNA ligase.

[972] This modified RNA preparation is used as a template for first strand cDNA synthesis using a gene specific oligonucleotide. The first strand synthesis reaction is used as a template for PCR amplification of the desired 5' end using a primer specific to the ligated RNA oligonucleotide and a primer specific to the known sequence of the gene of interest. The resultant product is then sequenced and analyzed to confirm that the 5' end sequence belongs to the desired gene.

Example 2: Isolation of Genomic Clones Corresponding to a Polynucleotide

[973] A human genomic P1 library (Genomic Systems, Inc.) is screened by PCR using primers selected for the cDNA sequence corresponding to SEQ ID NO:X., according to the method described in Example 1. (See also, Sambrook.)

Example 3: Tissue Distribution of Polypeptide

[974] Tissue distribution of mRNA expression of polynucleotides of the present invention is determined using protocols for Northern blot analysis, described by, among others, Sambrook et al. For example, a cDNA probe produced by the method described in Example 1 is labeled with P^{32} using the rediprime™ DNA labeling system (Amersham Life Science), according to manufacturer's instructions. After labeling, the probe is purified using CHROMA SPIN-100™ column (Clontech Laboratories, Inc.), according to manufacturer's protocol number PT1200-1. The purified labeled probe is then used to examine various human tissues for mRNA expression.

[975] Multiple Tissue Northern (MTN) blots containing various human tissues (H) or human immune system tissues (IM) (Clontech) are examined with the labeled probe using ExpressHyb™ hybridization solution (Clontech) according to manufacturer's protocol

number PT1190-1. Following hybridization and washing, the blots are mounted and exposed to film at -70°C overnight, and the films developed according to standard procedures.

Example 4: Chromosomal Mapping of the Polynucleotides

[976] An oligonucleotide primer set is designed according to the sequence at the 5' end of SEQ ID NO:X. This primer preferably spans about 100 nucleotides. This primer set is then used in a polymerase chain reaction under the following set of conditions : 30 seconds, 95°C; 1 minute, 56°C; 1 minute, 70°C. This cycle is repeated 32 times followed by one 5 minute cycle at 70°C. Human, mouse, and hamster DNA is used as template in addition to a somatic cell hybrid panel containing individual chromosomes or chromosome fragments (Bios, Inc). The reactions is analyzed on either 8% polyacrylamide gels or 3.5 % agarose gels. Chromosome mapping is determined by the presence of an approximately 100 bp PCR fragment in the particular somatic cell hybrid.

Example 5: Bacterial Expression of a Polypeptide

[977] A polynucleotide encoding a polypeptide of the present invention is amplified using PCR oligonucleotide primers corresponding to the 5' and 3' ends of the DNA sequence, as outlined in Example 1, to synthesize insertion fragments. The primers used to amplify the cDNA insert should preferably contain restriction sites, such as BamHI and XbaI and initiation/stop codons, if necessary, to clone the amplified product into the expression vector. For example, BamHI and XbaI correspond to the restriction enzyme sites on the bacterial expression vector pQE-9. (Qiagen, Inc., Chatsworth, CA). This plasmid vector encodes antibiotic resistance (Amp^r), a bacterial origin of replication (ori), an IPTG-regulatable promoter/operator (P/O), a ribosome binding site (RBS), a 6-histidine tag (6-His), and restriction enzyme cloning sites.

[978] The pQE-9 vector is digested with BamHI and XbaI and the amplified fragment is ligated into the pQE-9 vector maintaining the reading frame initiated at the bacterial RBS. The ligation mixture is then used to transform the E. coli strain M15/rep4 (Qiagen, Inc.) which contains multiple copies of the plasmid pREP4, which expresses the lacI repressor and also confers kanamycin resistance (Kan^r). Transformants are identified by their ability to

grow on LB plates and ampicillin/kanamycin resistant colonies are selected. Plasmid DNA is isolated and confirmed by restriction analysis.

[979] Clones containing the desired constructs are grown overnight (O/N) in liquid culture in LB media supplemented with both Amp (100 ug/ml) and Kan (25 ug/ml). The O/N culture is used to inoculate a large culture at a ratio of 1:100 to 1:250. The cells are grown to an optical density 600 (O.D.^{600}) of between 0.4 and 0.6. IPTG (Isopropyl-B-D-thiogalacto pyranoside) is then added to a final concentration of 1 mM. IPTG induces by inactivating the lacI repressor, clearing the P/O leading to increased gene expression.

[980] Cells are grown for an extra 3 to 4 hours. Cells are then harvested by centrifugation (20 mins at 6000Xg). The cell pellet is solubilized in the chaotropic agent 6 Molar Guanidine HCl by stirring for 3-4 hours at 4°C. The cell debris is removed by centrifugation, and the supernatant containing the polypeptide is loaded onto a nickel-nitrilo-tri-acetic acid ("Ni-NTA") affinity resin column (available from QIAGEN, Inc., *supra*). Proteins with a 6 x His tag bind to the Ni-NTA resin with high affinity and can be purified in a simple one-step procedure (for details see: The QIAexpressionist (1995) QIAGEN, Inc., *supra*).

[981] Briefly, the supernatant is loaded onto the column in 6 M guanidine-HCl, pH 8, the column is first washed with 10 volumes of 6 M guanidine-HCl, pH 8, then washed with 10 volumes of 6 M guanidine-HCl pH 6, and finally the polypeptide is eluted with 6 M guanidine-HCl, pH 5.

[982] The purified protein is then renatured by dialyzing it against phosphate-buffered saline (PBS) or 50 mM Na-acetate, pH 6 buffer plus 200 mM NaCl. Alternatively, the protein can be successfully refolded while immobilized on the Ni-NTA column. The recommended conditions are as follows: renature using a linear 6M-1M urea gradient in 500 mM NaCl, 20% glycerol, 20 mM Tris/HCl pH 7.4, containing protease inhibitors. The renaturation should be performed over a period of 1.5 hours or more. After renaturation the proteins are eluted by the addition of 250 mM immidazole. Immidazole is removed by a final dialyzing step against PBS or 50 mM sodium acetate pH 6 buffer plus 200 mM NaCl. The purified protein is stored at 4° C or frozen at -80° C.

[983] In addition to the above expression vector, the present invention further includes an expression vector comprising phage operator and promoter elements operatively linked to a polynucleotide of the present invention, called pHE4a. (ATCC Accession Number 209645,

deposited on February 25, 1998.) This vector contains: 1) a neomycinphosphotransferase gene as a selection marker, 2) an E. coli origin of replication, 3) a T5 phage promoter sequence, 4) two lac operator sequences, 5) a Shine-Delgarno sequence, and 6) the lactose operon repressor gene (lacIq). The origin of replication (oriC) is derived from pUC19 (LTI, Gaithersburg, MD). The promoter sequence and operator sequences are made synthetically.

[984] DNA can be inserted into the pHEa by restricting the vector with NdeI and XbaI, BamHI, XhoI, or Asp718, running the restricted product on a gel, and isolating the larger fragment (the stuffer fragment should be about 310 base pairs). The DNA insert is generated according to the PCR protocol described in Example 1, using PCR primers having restriction sites for NdeI (5' primer) and XbaI, BamHI, XhoI, or Asp718 (3' primer). The PCR insert is gel purified and restricted with compatible enzymes. The insert and vector are ligated according to standard protocols.

[985] The engineered vector could easily be substituted in the above protocol to express protein in a bacterial system.

Example 6: Purification of a Polypeptide from an Inclusion Body

[986] The following alternative method can be used to purify a polypeptide expressed in *E coli* when it is present in the form of inclusion bodies. Unless otherwise specified, all of the following steps are conducted at 4-10°C.

[987] Upon completion of the production phase of the *E. coli* fermentation, the cell culture is cooled to 4-10°C and the cells harvested by continuous centrifugation at 15,000 rpm (Heraeus Sepatech). On the basis of the expected yield of protein per unit weight of cell paste and the amount of purified protein required, an appropriate amount of cell paste, by weight, is suspended in a buffer solution containing 100 mM Tris, 50 mM EDTA, pH 7.4. The cells are dispersed to a homogeneous suspension using a high shear mixer.

[988] The cells are then lysed by passing the solution through a microfluidizer (Microfuidics, Corp. or APV Gaulin, Inc.) twice at 4000-6000 psi. The homogenate is then mixed with NaCl solution to a final concentration of 0.5 M NaCl, followed by centrifugation at 7000 xg for 15 min. The resultant pellet is washed again using 0.5M NaCl, 100 mM Tris, 50 mM EDTA, pH 7.4.

[989] The resulting washed inclusion bodies are solubilized with 1.5 M guanidine hydrochloride (GuHCl) for 2-4 hours. After 7000 xg centrifugation for 15 min., the pellet is

discarded and the polypeptide containing supernatant is incubated at 4°C overnight to allow further GuHCl extraction.

[990] Following high speed centrifugation (30,000 xg) to remove insoluble particles, the GuHCl solubilized protein is refolded by quickly mixing the GuHCl extract with 20 volumes of buffer containing 50 mM sodium, pH 4.5, 150 mM NaCl, 2 mM EDTA by vigorous stirring. The refolded diluted protein solution is kept at 4°C without mixing for 12 hours prior to further purification steps.

[991] To clarify the refolded polypeptide solution, a previously prepared tangential filtration unit equipped with 0.16 μm membrane filter with appropriate surface area (e.g., Filtron), equilibrated with 40 mM sodium acetate, pH 6.0 is employed. The filtered sample is loaded onto a cation exchange resin (e.g., Poros HS-50, Perseptive Biosystems). The column is washed with 40 mM sodium acetate, pH 6.0 and eluted with 250 mM, 500 mM, 1000 mM, and 1500 mM NaCl in the same buffer, in a stepwise manner. The absorbance at 280 nm of the effluent is continuously monitored. Fractions are collected and further analyzed by SDS-PAGE.

[992] Fractions containing the polypeptide are then pooled and mixed with 4 volumes of water. The diluted sample is then loaded onto a previously prepared set of tandem columns of strong anion (Poros HQ-50, Perseptive Biosystems) and weak anion (Poros CM-20, Perseptive Biosystems) exchange resins. The columns are equilibrated with 40 mM sodium acetate, pH 6.0. Both columns are washed with 40 mM sodium acetate, pH 6.0, 200 mM NaCl. The CM-20 column is then eluted using a 10 column volume linear gradient ranging from 0.2 M NaCl, 50 mM sodium acetate, pH 6.0 to 1.0 M NaCl, 50 mM sodium acetate, pH 6.5. Fractions are collected under constant A_{280} monitoring of the effluent. Fractions containing the polypeptide (determined, for instance, by 16% SDS-PAGE) are then pooled.

[993] The resultant polypeptide should exhibit greater than 95% purity after the above refolding and purification steps. No major contaminant bands should be observed from Commassie blue stained 16% SDS-PAGE gel when 5 μg of purified protein is loaded. The purified protein can also be tested for endotoxin/LPS contamination, and typically the LPS content is less than 0.1 ng/ml according to LAL assays.

Example 7: Cloning and Expression of a Polypeptide in a Baculovirus Expression System

[994] In this example, the plasmid shuttle vector pA2 is used to insert a polynucleotide into a baculovirus to express a polypeptide. This expression vector contains the strong polyhedrin promoter of the *Autographa californica* nuclear polyhedrosis virus (AcMNPV) followed by convenient restriction sites such as BamHI, Xba I and Asp718. The polyadenylation site of the simian virus 40 ("SV40") is used for efficient polyadenylation. For easy selection of recombinant virus, the plasmid contains the beta-galactosidase gene from *E. coli* under control of a weak Drosophila promoter in the same orientation, followed by the polyadenylation signal of the polyhedrin gene. The inserted genes are flanked on both sides by viral sequences for cell-mediated homologous recombination with wild-type viral DNA to generate a viable virus that express the cloned polynucleotide.

[995] Many other baculovirus vectors can be used in place of the vector above, such as pAc373, pVL941, and pAcIM1, as one skilled in the art would readily appreciate, as long as the construct provides appropriately located signals for transcription, translation, secretion and the like, including a signal peptide and an in-frame AUG as required. Such vectors are described, for instance, in Luckow et al., Virology 170:31-39 (1989).

[996] Specifically, the cDNA sequence contained in the deposited clone is amplified using the PCR protocol described in Example 1 using primers with appropriate restriction sites and initiation/stop codons. If the naturally occurring signal sequence is used to produce the secreted protein, the pA2 vector does not need a second signal peptide. Alternatively, the vector can be modified (pA2 GP) to include a baculovirus leader sequence, using the standard methods described in Summers et al., "A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures," Texas Agricultural Experimental Station Bulletin NO: 1555 (1987).

[997] The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("Geneclean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

[998] The plasmid is digested with the corresponding restriction enzymes and optionally, can be dephosphorylated using calf intestinal phosphatase, using routine procedures known in the art. The DNA is then isolated from a 1% agarose gel using a commercially available kit ("Geneclean" BIO 101 Inc., La Jolla, Ca.).

[999] The fragment and the dephosphorylated plasmid are ligated together with T4 DNA ligase. *E. coli* HB101 or other suitable *E. coli* hosts such as XL-1 Blue (Stratagene Cloning Systems, La Jolla, CA) cells are transformed with the ligation mixture and spread on culture plates. Bacteria containing the plasmid are identified by digesting DNA from individual colonies and analyzing the digestion product by gel electrophoresis. The sequence of the cloned fragment is confirmed by DNA sequencing.

[1000] Five µg of a plasmid containing the polynucleotide is co-transfected with 1.0 µg of a commercially available linearized baculovirus DNA ("BaculoGold™ baculovirus DNA", Pharmingen, San Diego, CA), using the lipofection method described by Felgner et al., Proc. Natl. Acad. Sci. USA 84:7413-7417 (1987). One µg of BaculoGold™ virus DNA and 5 µg of the plasmid are mixed in a sterile well of a microtiter plate containing 50 µl of serum-free Grace's medium (Life Technologies Inc., Gaithersburg, MD). Afterwards, 10 µl Lipofectin plus 90 µl Grace's medium are added, mixed and incubated for 15 minutes at room temperature. Then the transfection mixture is added drop-wise to Sf9 insect cells (ATCC CRL 1711) seeded in a 35 mm tissue culture plate with 1 ml Grace's medium without serum. The plate is then incubated for 5 hours at 27° C. The transfection solution is then removed from the plate and 1 ml of Grace's insect medium supplemented with 10% fetal calf serum is added. Cultivation is then continued at 27° C for four days.

[1001] After four days the supernatant is collected and a plaque assay is performed, as described by Summers and Smith, *supra*. An agarose gel with "Blue Gal" (Life Technologies Inc., Gaithersburg) is used to allow easy identification and isolation of gal-expressing clones, which produce blue-stained plaques. (A detailed description of a "plaque assay" of this type can also be found in the user's guide for insect cell culture and baculovirology distributed by Life Technologies Inc., Gaithersburg, page 9-10.) After appropriate incubation, blue stained plaques are picked with the tip of a micropipettor (e.g., Eppendorf). The agar containing the recombinant viruses is then resuspended in a microcentrifuge tube containing 200 µl of Grace's medium and the suspension containing the recombinant baculovirus is used to infect Sf9 cells seeded in 35 mm dishes. Four days later the supernatants of these culture dishes are harvested and then they are stored at 4° C.

[1002] To verify the expression of the polypeptide, Sf9 cells are grown in Grace's medium supplemented with 10% heat-inactivated FBS. The cells are infected with the recombinant baculovirus containing the polynucleotide at a multiplicity of infection ("MOI") of about 2.

If radiolabeled proteins are desired, 6 hours later the medium is removed and is replaced with SF900 II medium minus methionine and cysteine (available from Life Technologies Inc., Rockville, MD). After 42 hours, 5 μCi of ^{35}S-methionine and 5 μCi ^{35}S-cysteine (available from Amersham) are added. The cells are further incubated for 16 hours and then are harvested by centrifugation. The proteins in the supernatant as well as the intracellular proteins are analyzed by SDS-PAGE followed by autoradiography (if radiolabeled).

[1003] Microsequencing of the amino acid sequence of the amino terminus of purified protein may be used to determine the amino terminal sequence of the produced protein.

Example 8: Expression of a Polypeptide in Mammalian Cells

[1004] The polypeptide of the present invention can be expressed in a mammalian cell. A typical mammalian expression vector contains a promoter element, which mediates the initiation of transcription of mRNA, a protein coding sequence, and signals required for the termination of transcription and polyadenylation of the transcript. Additional elements include enhancers, Kozak sequences and intervening sequences flanked by donor and acceptor sites for RNA splicing. Highly efficient transcription is achieved with the early and late promoters from SV40, the long terminal repeats (LTRs) from Retroviruses, e.g., RSV, HTLVI, HIVI and the early promoter of the cytomegalovirus (CMV). However, cellular elements can also be used (e.g., the human actin promoter).

[1005] Suitable expression vectors for use in practicing the present invention include, for example, vectors such as pSVL and pMSG (Pharmacia, Uppsala, Sweden), pRSVcat (ATCC 37152), pSV2dhfr (ATCC 37146), pBC12MI (ATCC 67109), pCMVSport 2.0, and pCMVSport 3.0. Mammalian host cells that could be used include, human Hela, 293, H9 and Jurkat cells, mouse NIH3T3 and C127 cells, Cos 1, Cos 7 and CV1, quail QC1-3 cells, mouse L cells and Chinese hamster ovary (CHO) cells.

[1006] Alternatively, the polypeptide can be expressed in stable cell lines containing the polynucleotide integrated into a chromosome. The co-transfection with a selectable marker such as dhfr, gpt, neomycin, hygromycin allows the identification and isolation of the transfected cells.

[1007] The transfected gene can also be amplified to express large amounts of the encoded protein. The DHFR (dihydrofolate reductase) marker is useful in developing cell lines that carry several hundred or even several thousand copies of the gene of interest. (See, e.g., Alt et

al., *J. Biol. Chem.*, 253:1357-1370 (1978); Hamlin et al., *Biochem. et Biophys. Acta*, 1097:107-143 (1990); Page et al., *Biotechnology*, 9:64-68 (1991)). Another useful selection marker is the enzyme glutamine synthase (GS) (Murphy et al., *Biochem J.*, 227:277-279 (1991); Bebbington et al., *Bio/Technology*, 10:169-175 (1992). Using these markers, the mammalian cells are grown in selective medium and the cells with the highest resistance are selected. These cell lines contain the amplified gene(s) integrated into a chromosome. Chinese hamster ovary (CHO) and NSO cells are often used for the production of proteins.

[1008] Derivatives of the plasmid pSV2-dhfr (ATCC Accession No.: 37146), the expression vectors pC4 (ATCC Accession No.: 209646) and pC6 (ATCC Accession No.:209647) contain the strong promoter (LTR) of the Rous Sarcoma Virus (Cullen et al., *Molecular and Cellular Biology*, 438-447 (March, 1985)) plus a fragment of the CMV-enhancer (Boshart et al., *Cell*, 41:521-530 (1985)). Multiple cloning sites, e.g., with the restriction enzyme cleavage sites BamHI, XbaI and Asp718, facilitate the cloning of the gene of interest. The vectors also contain the 3' intron, the polyadenylation and termination signal of the rat preproinsulin gene, and the mouse DHFR gene under control of the SV40 early promoter.

[1009] Specifically, the plasmid pC6, for example, is digested with appropriate restriction enzymes and then dephosphorylated using calf intestinal phosphates by procedures known in the art. The vector is then isolated from a 1% agarose gel.

[1010] A polynucleotide of the present invention is amplified according to the protocol outlined in Example 1 using primers with appropriate restrictions sites and initiation/stop codons, if necessary. The vector can be modified to include a heterologous signal sequence if necessary for secretion. (See, e.g., WO 96/34891.)

[1011] The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("Geneclean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

[1012] The amplified fragment is then digested with the same restriction enzyme and purified on a 1% agarose gel. The isolated fragment and the dephosphorylated vector are then ligated with T4 DNA ligase. *E. coli* HB101 or XL-1 Blue cells are then transformed and bacteria are identified that contain the fragment inserted into plasmid pC6 using, for instance, restriction enzyme analysis.

[1013] Chinese hamster ovary cells lacking an active DHFR gene is used for transfection. Five µg of the expression plasmid pC6 is cotransfected with 0.5 µg of the plasmid pSVneo using lipofectin (Felgner et al., *supra*). The plasmid pSV2-neo contains a dominant selectable marker, the *neo* gene from Tn5 encoding an enzyme that confers resistance to a group of antibiotics including G418. The cells are seeded in alpha minus MEM supplemented with 1 mg/ml G418. After 2 days, the cells are trypsinized and seeded in hybridoma cloning plates (Greiner, Germany) in alpha minus MEM supplemented with 10, 25, or 50 ng/ml of metothrexate plus 1 mg/ml G418. After about 10-14 days single clones are trypsinized and then seeded in 6-well petri dishes or 10 ml flasks using different concentrations of methotrexate (50 nM, 100 nM, 200 nM, 400 nM, 800 nM). Clones growing at the highest concentrations of methotrexate are then transferred to new 6-well plates containing even higher concentrations of methotrexate (1 µM, 2 µM, 5 µM, 10 mM, 20 mM). The same procedure is repeated until clones are obtained which grow at a concentration of 100 - 200 µM. Expression of the desired gene product is analyzed, for instance, by SDS-PAGE and Western blot or by reversed phase HPLC analysis.

Example 9: Protein Fusions

[1014] The polypeptides of the present invention are preferably fused to other proteins. These fusion proteins can be used for a variety of applications. For example, fusion of the present polypeptides to His-tag, HA-tag, protein A, IgG domains, and maltose binding protein facilitates purification. (See Example 5; see also EP A 394,827; Traunecker, et al., *Nature,* 331:84-86 (1988)) The polypeptides can also be fused to heterologous polypeptide sequences to facilitate secretion and intracellular trafficking (e.g., KDEL). Moreover, fusion to IgG-1, IgG-3, and albumin increases the halflife time in vivo. Nuclear localization signals fused to the polypeptides of the present invention can target the protein to a specific subcellular localization, while covalent heterodimer or homodimers can increase or decrease the activity of a fusion protein. Fusion proteins can also create chimeric molecules having more than one function. Finally, fusion proteins can increase solubility and/or stability of the fused protein compared to the non-fused protein. All of the types of fusion proteins described above can be made by modifying the following protocol, which outlines the fusion of a polypeptide to an IgG molecule, or the protocol described in Example 5.

[1015] Briefly, the human Fc portion of the IgG molecule can be PCR amplified, using primers that span the 5' and 3' ends of the sequence described below. These primers also should have convenient restriction enzyme sites that will facilitate cloning into an expression vector, preferably a mammalian expression vector, and initiation/stop codons, if necessary.

[1016] For example, if pC4 (Accession No.: 209646) is used, the human Fc portion can be ligated into the BamHI cloning site. Note that the 3' BamHI site should be destroyed. Next, the vector containing the human Fc portion is re-restricted with BamHI, linearizing the vector, and a polynucleotide of the present invention, isolated by the PCR protocol described in Example 1, is ligated into this BamHI site. Note that the polynucleotide is cloned without a stop codon, otherwise a fusion protein will not be produced.

[1017] If the naturally occurring signal sequence is used to produce the secreted protein, pC4 does not need a second signal peptide. Alternatively, if the naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., WO 96/34891.)

Human IgG Fc region:

GGGATCCGGAGCCCAAATCTTCTGACAAAACTCACACATGCCCACCGTGCCCAGCACCTGAATTCG
AGGGTGCACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAAGGACACCCTCATGATCTCCCGGACTC
CTGAGGTCACATGCGTGGTGGTGGACGTAAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTAC
GTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGT
ACCGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGC
AAGGTCTCCAACAAAGCCCTCCCAACCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCAGCC
CCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCC
TGACCTGCCTGGTCAAAGGCTTCTATCCAAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAG
CCGGAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCCTCTACAGC
AAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGA
GGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAATGAGTGCGACGGC
CGCGACTCTAGAGGAT (SEQ ID NO:1)

Example 10: Formulating a Polypeptide

[1018] The invention also provides methods of treatment and/or prevention of diseases or disorders (such as, for example, any one or more of the diseases or disorders disclosed herein) by administration to a subject of an effective amount of a Therapeutic. By Therapeutic is meant polynucleotides or polypeptides of the invention (including fragments

and variants), agonists or antagonists thereof, and/or antibodies thereto, in combination with a pharmaceutically acceptable carrier type (e.g., a sterile carrier).

[1019] The polypeptide composition will be formulated and dosed in a fashion consistent with good medical practice, taking into account the clinical condition of the individual patient (especially the side effects of treatment with the secreted polypeptide alone), the site of delivery, the method of administration, the scheduling of administration, and other factors known to practitioners. The "effective amount" for purposes herein is thus determined by such considerations.

[1020] As a general proposition, the total pharmaceutically effective amount of polypeptide administered parenterally per dose will be in the range of about 1 μg/kg/day to 10 mg/kg/day of patient body weight, although, as noted above, this will be subject to therapeutic discretion. More preferably, this dose is at least 0.01 mg/kg/day, and most preferably for humans between about 0.01 and 1 mg/kg/day for the hormone. If given continuously, the polypeptide is typically administered at a dose rate of about 1 μg/kg/hour to about 50 μg/kg/hour, either by 1-4 injections per day or by continuous subcutaneous infusions, for example, using a mini-pump. An intravenous bag solution may also be employed. The length of treatment needed to observe changes and the interval following treatment for responses to occur appears to vary depending on the desired effect.

[1021] Pharmaceutical compositions containing the polypeptide of the invention are administered orally, rectally, parenterally, intracistemally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), bucally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. The term "parenteral" as used herein refers to modes of administration which include intravenous

277 (1981), and Langer, *Chem. Tech.*, 12:98-105 (1982)), ethylene vinyl acetate (R. Langer et al.) or poly-D- (-)-3-hydroxybutyric acid (EP 133,988). Sustained-release compositions also include liposomally entrapped polypeptides. Liposomes containing the secreted polypeptide are prepared by methods known per se: DE 3,218,121; Epstein et al., *Proc. Natl. Acad. Sci. USA*, 82:3688-3692 (1985); Hwang et al., *Proc. Natl. Acad. Sci. USA* , 77:4030-4034 (1980); EP 52,322; EP 36,676; EP 88,046; EP 143,949; EP 142,641; Japanese Pat. Appl. 83-118008; U.S. Pat. Nos. 4,485,045 and 4,544,545; and EP 102,324. Ordinarily, the liposomes are of the small (about 200-800 Angstroms) unilamellar type in which the lipid content is greater than about 30 mol. percent cholesterol, the selected proportion being adjusted for the optimal secreted polypeptide therapy.

[1023] For parenteral administration, in one embodiment, the polypeptide is formulated generally by mixing it at the desired degree of purity, in a unit dosage injectable form (solution, suspension, or emulsion), with a pharmaceutically acceptable carrier, i.e., one that is non-toxic to recipients at the dosages and concentrations employed and is compatible with other ingredients of the formulation. For example, the formulation preferably does not include oxidizing agents and other compounds that are known to be deleterious to polypeptides.

[1024] Generally, the formulations are prepared by contacting the polypeptide uniformly and intimately with liquid carriers or finely divided solid carriers or both. Then, if necessary, the product is shaped into the desired formulation. Preferably the carrier is a parenteral carrier, more preferably a solution that is isotonic with the blood of the recipient. Examples of such carrier vehicles include water, saline, Ringer's solution, and dextrose solution. Non-aqueous vehicles such as fixed oils and ethyl oleate are also useful herein, as well as liposomes.

[1025] The carrier suitably contains minor amounts of additives such as substances that enhance isotonicity and chemical stability. Such materials are non-toxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, succinate, acetic acid, and other organic acids or their salts; antioxidants such as ascorbic acid; low molecular weight (less than about ten residues) polypeptides, e.g., polyarginine or tripeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids, such as glycine, glutamic acid, aspartic acid, or arginine; monosaccharides, disaccharides, and other carbohydrates including

cellulose or its derivatives, glucose, manose, or dextrins; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; counterions such as sodium; and/or nonionic surfactants such as polysorbates, poloxamers, or PEG.

[1026] The polypeptide is typically formulated in such vehicles at a concentration of about 0.1 mg/ml to 100 mg/ml, preferably 1-10 mg/ml, at a pH of about 3 to 8. It will be understood that the use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of polypeptide salts.

[1027] Any polypeptide to be used for therapeutic administration can be sterile. Sterility is readily accomplished by filtration through sterile filtration membranes (e.g., 0.2 micron membranes). Therapeutic polypeptide compositions generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

[1028] Polypeptides ordinarily will be stored in unit or multi-dose containers, for example, sealed ampoules or vials, as an aqueous solution or as a lyophilized formulation for reconstitution. As an example of a lyophilized formulation, 10-ml vials are filled with 5 ml of sterile-filtered 1% (w/v) aqueous polypeptide solution, and the resulting mixture is lyophilized. The infusion solution is prepared by reconstituting the lyophilized polypeptide using bacteriostatic Water-for-Injection.

[1029] The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration. In addition, the polypeptides of the present invention may be employed in conjunction with other therapeutic compounds.

[1030] The Therapeutics of the invention may be administered alone or in combination with adjuvants. Adjuvants that may be administered with the Therapeutics of the invention include, but are not limited to, alum, alum plus deoxycholate (ImmunoAg), MTP-PE (Biocine Corp.), QS21 (Genentech, Inc.), BCG (e.g., THERACYS®), MPL and nonviable prepartions of *Corynebacterium parvum*. In a specific embodiment, Therapeutics of the invention are administered in combination with alum. In another specific embodiment, Therapeutics of the invention are administered in combination with QS-21. Further adjuvants that may be

administered with the Therapeutics of the invention include, but are not limited to, Monophosphoryl lipid immunomodulator, AdjuVax 100a, QS-21, QS-18, CRL1005, Aluminum salts, MF-59, and Virosomal adjuvant technology. Vaccines that may be administered with the Therapeutics of the invention include, but are not limited to, vaccines directed toward protection against MMR (measles, mumps, rubella), polio, varicella, tetanus/diptheria, hepatitis A, hepatitis B, haemophilus influenzae B, whooping cough, pneumonia, influenza, Lyme's Disease, rotavirus, cholera, yellow fever, Japanese encephalitis, poliomyelitis, rabies, typhoid fever, and pertussis. Combinations may be administered either concomitantly, e.g., as an admixture, separately but simultaneously or concurrently; or sequentially. This includes presentations in which the combined agents are administered together as a therapeutic mixture, and also procedures in which the combined agents are administered separately but simultaneously, e.g., as through separate intravenous lines into the same individual. Administration "in combination" further includes the separate administration of one of the compounds or agents given first, followed by the second.

[1031] The Therapeutics of the invention may be administered alone or in combination with other therapeutic agents. Therapeutic agents that may be administered in combination with the Therapeutics of the invention, include but not limited to, chemotherapeutic agents, antibiotics, steroidal and non-steroidal anti-inflammatories, conventional immunotherapeutic agents, and/or therapeutic treatments described below. Combinations may be administered either concomitantly, e.g., as an admixture, separately but simultaneously or concurrently; or sequentially. This includes presentations in which the combined agents are administered together as a therapeutic mixture, and also procedures in which the combined agents are administered separately but simultaneously, e.g., as through separate intravenous lines into the same individual. Administration "in combination" further includes the separate administration of one of the compounds or agents given first, followed by the second.

[1032] In one embodiment, the Therapeutics of the invention are administered in combination with an anticoagulant. Anticoagulants that may be administered with the compositions of the invention include, but are not limited to, heparin, low molecular weight heparin, warfarin sodium (e.g., COUMADIN®), dicumarol, 4-hydroxycoumarin, anisindione (e.g., MIRADON™), acenocoumarol (e.g., nicoumalone, SINTHROME™), indan-1,3-dione, phenprocoumon (e.g., MARCUMAR™), ethyl biscoumacetate (e.g., TROMEXAN™), and aspirin. In a specific embodiment, compositions of the invention are administered in

combination with heparin and/or warfarin. In another specific embodiment, compositions of the invention are administered in combination with warfarin. In another specific embodiment, compositions of the invention are administered in combination with warfarin and aspirin. In another specific embodiment, compositions of the invention are administered in combination with heparin. In another specific embodiment, compositions of the invention are administered in combination with heparin and aspirin.

[1033] In another embodiment, the Therapeutics of the invention are administered in combination with thrombolytic drugs. Thrombolytic drugs that may be administered with the compositions of the invention include, but are not limited to, plasminogen, lys-plasminogen, alpha2-antiplasmin, streptokinae (e.g., KABIKINASE™), antiresplace (e.g., EMINASE™), tissue plasminogen activator (t-PA, altevase, ACTIVASE™), urokinase (e.g., ABBOKINASE™), sauruplase, (Prourokinase, single chain urokinase), and aminocaproic acid (e.g., AMICAR™). In a specific embodiment, compositions of the invention are administered in combination with tissue plasminogen activator and aspirin.

[1034] In another embodiment, the Therapeutics of the invention are administered in combination with antiplatelet drugs. Antiplatelet drugs that may be administered with the compositions of the invention include, but are not limited to, aspirin, dipyridamole (e.g., PERSANTINE™), and ticlopidine (e.g., TICLID™).

[1035] In specific embodiments, the use of anti-coagulants, thrombolytic and/or antiplatelet drugs in combination with Therapeutics of the invention is contemplated for the prevention, diagnosis, and/or treatment of thrombosis, arterial thrombosis, venous thrombosis, thromboembolism, pulmonary embolism, atherosclerosis, myocardial infarction, transient ischemic attack, unstable angina. In specific embodiments, the use of anticoagulants, thrombolytic drugs and/or antiplatelet drugs in combination with Therapeutics of the invention is contemplated for the prevention of occulsion of saphenous grafts, for reducing the risk of periprocedural thrombosis as might accompany angioplasty procedures, for reducing the risk of stroke in patients with atrial fibrillation including nonrheumatic atrial fibrillation, for reducing the risk of embolism associated with mechanical heart valves and or mitral valves disease. Other uses for the therapeutics of the invention, alone or in combination with antiplatelet, anticoagulant, and/or thrombolytic drugs, include, but are not limited to, the prevention of occlusions in extracorporeal devices (e.g., intravascular canulas, vascular access shunts in hemodialysis patients, hemodialysis machines, and

cardiopulmonary bypass machines).

[1036] In certain embodiments, Therapeutics of the invention are administered in combination with antiretroviral agents, nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and/or protease inhibitors (PIs). NRTIs that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, RETROVIR™ (zidovudine/AZT), VIDEX™ (didanosine/ddI), HIVID™ (zalcitabine/ddC), ZERIT™ (stavudine/d4T), EPIVIR™ (lamivudine/3TC), and COMBIVIR™ (zidovudine/lamivudine). NNRTIs that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, VIRAMUNE™ (nevirapine), RESCRIPTOR™ (delavirdine), and SUSTIVA™ (efavirenz). Protease inhibitors that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, CRIXIVAN™ (indinavir), NORVIR™ (ritonavir), INVIRASE™ (saquinavir), and VIRACEPT™ (nelfinavir). In a specific embodiment, antiretroviral agents, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and/or protease inhibitors may be used in any combination with Therapeutics of the invention to treat AIDS and/or to prevent or treat HIV infection.

[1037] Additional NRTIs include LODENOSINE™ (F-ddA; an acid-stable adenosine NRTI; Triangle/Abbott; COVIRACIL™ (emtricitabine/FTC; structurally related to lamivudine (3TC) but with 3- to 10-fold greater activity *in vitro*; Triangle/Abbott); dOTC (BCH-10652, also structurally related to lamivudine but retains activity against a substantial proportion of lamivudine-resistant isolates; Biochem Pharma); Adefovir (refused approval for anti-HIV therapy by FDA; Gilead Sciences); PREVEON® (Adefovir Dipivoxil, the active prodrug of adefovir; its active form is PMEA-pp); TENOFOVIR™ (bis-POC PMPA, a PMPA prodrug; Gilead); DAPD/DXG (active metabolite of DAPD; Triangle/Abbott); D-D4FC (related to 3TC, with activity against AZT/3TC-resistant virus); GW420867X (Glaxo Wellcome); ZIAGEN™ (abacavir/159U89; Glaxo Wellcome Inc.); CS-87 (3'azido-2',3'-dideoxyuridine; WO 99/66936); and S-acyl-2-thioethyl (SATE)-bearing prodrug forms of β-L-FD4C and β-L-FddC (WO 98/17281).

[1038] Additional NNRTIs include COACTINON™ (Emivirine/MKC-442, potent NNRTI of the HEPT class; Triangle/Abbott); CAPRAVIRINE™ (AG-1549/S-1153, a next generation

NNRTI with activity against viruses containing the K103N mutation; Agouron); PNU-142721 (has 20- to 50-fold greater activity than its predecessor delavirdine and is active against K103N mutants; Pharmacia & Upjohn); DPC-961 and DPC-963 (second-generation derivatives of efavirenz, designed to be active against viruses with the K103N mutation; DuPont); GW-420867X (has 25-fold greater activity than HBY097 and is active against K103N mutants; Glaxo Wellcome); CALANOLIDE A (naturally occurring agent from the latex tree; active against viruses containing either or both the Y181C and K103N mutations); and Propolis (WO 99/49830).

[1039] Additional protease inhibitors include LOPINAVIR™ (ABT378/r; Abbott Laboratories); BMS-232632 (an azapeptide; Bristol-Myres Squibb); TIPRANAVIR™ (PNU-140690, a non-peptic dihydropyrone; Pharmacia & Upjohn); PD-178390 (a nonpeptidic dihydropyrone; Parke-Davis); BMS 232632 (an azapeptide; Bristol-Myers Squibb); L-756,423 (an indinavir analog; Merck); DMP-450 (a cyclic urea compound; Avid & DuPont); AG-1776 (a peptidomimetic with *in vitro* activity against protease inhibitor-resistant viruses; Agouron); VX-175/GW-433908 (phosphate prodrug of amprenavir; Vertex & Glaxo Welcome); CGP61755 (Ciba); and AGENERASE™ (amprenavir; Glaxo Wellcome Inc.).

[1040] Additional antiretroviral agents include fusion inhibitors/gp41 binders. Fusion inhibitors/gp41 binders include T-20 (a peptide from residues 643-678 of the HIV gp41 transmembrane protein ectodomain which binds to gp41 in its resting state and prevents transformation to the fusogenic state; Trimeris) and T-1249 (a second-generation fusion inhibitor; Trimeris).

[1041] Additional antiretroviral agents include fusion inhibitors/chemokine receptor antagonists. Fusion inhibitors/chemokine receptor antagonists include CXCR4 antagonists such as AMD 3100 (a bicyclam), SDF-1 and its analogs, and ALX40-4C (a cationic peptide), T22 (an 18 amino acid peptide; Trimeris) and the T22 analogs T134 and T140; CCR5 antagonists such as RANTES (9-68), AOP-RANTES, NNY-RANTES, and TAK-779; and CCR5/CXCR4 antagonists such as NSC 651016 (a distamycin analog). Also included are CCR2B, CCR3, and CCR6 antagonists. Chemokine recpetor agonists such as RANTES, SDF-1, MIP-1α, MIP-1β, etc., may also inhibit fusion.

[1042] Additional antiretroviral agents include integrase inhibitors. Integrase inhibitors include dicaffeoylquinic (DFQA) acids; L-chicoric acid (a dicaffeoyltartaric (DCTA) acid);

quinalizarin (QLC) and related anthraquinones; ZINTEVIR™ (AR 177, an oligonucleotide that probably acts at cell surface rather than being a true integrase inhibitor; Arondex); and naphthols such as those disclosed in WO 98/50347.

[1043] Additional antiretroviral agents include hydroxyurea-like compunds such as BCX-34 (a purine nucleoside phosphorylase inhibitor; Biocryst); ribonucleotide reductase inhibitors such as DIDOX™ (Molecules for Health); inosine monophosphate dehydrogenase (IMPDH) inhibitors sucha as VX-497 (Vertex); and mycopholic acids such as CellCept (mycophenolate mofetil; Roche).

[1044] Additional antiretroviral agents include inhibitors of viral integrase, inhibitors of viral genome nuclear translocation such as arylene bis(methylketone) compounds; inhibitors of HIV entry such as AOP-RANTES, NNY-RANTES, RANTES-IgG fusion protein, soluble complexes of RANTES and glycosaminoglycans (GAG), and AMD-3100; nucleocapsid zinc finger inhibitors such as dithiane compounds; targets of HIV Tat and Rev; and pharmacoenhancers such as ABT-378.

[1045] Other antiretroviral therapies and adjunct therapies include cytokines and lymphokines such as MIP-1α, MIP-1β, SDF-1α, IL-2, PROLEUKIN™ (aldesleukin/L2-7001; Chiron), IL-4, IL-10, IL-12, and IL-13; interferons such as IFN-α2a; antagonists of TNFs, NFκB, GM-CSF, M-CSF, and IL-10; agents that modulate immune activation such as cyclosporin and prednisone; vaccines such as Remune™ (HIV Immunogen), APL 400-003 (Apollon), recombinant gp120 and fragments, bivalent (B/E) recombinant envelope glycoprotein, rgp120CM235, MN rgp120, SF-2 rgp120, gp120/soluble CD4 complex, Delta JR-FL protein, branched synthetic peptide derived from discontinuous gp120 C3/C4 domain, fusion-competent immunogens, and Gag, Pol, Nef, and Tat vaccines; gene-based therapies such as genetic suppressor elements (GSEs; WO 98/54366), and intrakines (genetically modified CC chemokines targetted to the ER to block surface expression of newly synthesized CCR5 (Yang *et al., PNAS 94*:11567-72 (1997); Chen *et al., Nat. Med. 3*:1110-16 (1997)); antibodies such as the anti-CXCR4 antibody 12G5, the anti-CCR5 antibodies 2D7, 5C7, PA8, PA9, PA10, PA11, PA12, and PA14, the anti-CD4 antibodies Q4120 and RPA-T4, the anti-CCR3 antibody 7B11, the anti-gp120 antibodies 17b, 48d, 447-52D, 257-D, 268-D and 50.1, anti-Tat antibodies, anti-TNF-α antibodies, and monoclonal antibody 33A; aryl hydrocarbon (AH) receptor agonists and antagonists such as TCDD, 3,3',4,4',5-

pentachlorobiphenyl, 3,3',4,4'-tetrachlorobiphenyl, and α-naphthoflavone (WO 98/30213); and antioxidants such as γ-L-glutamyl-L-cysteine ethyl ester (γ-GCE; WO 99/56764).

[1046] In a further embodiment, the Therapeutics of the invention are administered in combination with an antiviral agent. Antiviral agents that may be administered with the Therapeutics of the invention include, but are not limited to, acyclovir, ribavirin, amantadine, and remantidine.

[1047] In other embodiments, Therapeutics of the invention may be administered in combination with anti-opportunistic infection agents. Anti-opportunistic agents that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, TRIMETHOPRIM-SULFAMETHOXAZOLE™, DAPSONE™, PENTAMIDINE™, ATOVAQUONE™, ISONIAZID™, RIFAMPIN™, PYRAZINAMIDE™, ETHAMBUTOL™, RIFABUTIN™, CLARITHROMYCIN™, AZITHROMYCIN™, GANCICLOVIR™, FOSCARNET™, CIDOFOVIR™, FLUCONAZOLE™, ITRACONAZOLE™, KETOCONAZOLE™, ACYCLOVIR™, FAMCICOLVIR™, PYRIMETHAMINE™, LEUCOVORIN™, NEUPOGEN™ (filgrastim/G-CSF), and LEUKINE™ (sargramostim/GM-CSF). In a specific embodiment, Therapeutics of the invention are used in any combination with TRIMETHOPRIM-SULFAMETHOXAZOLE™, DAPSONE™, PENTAMIDINE™, and/or ATOVAQUONE™ to prophylactically treat or prevent an opportunistic *Pneumocystis carinii* pneumonia infection. In another specific embodiment, Therapeutics of the invention are used in any combination with ISONIAZID™, RIFAMPIN™, PYRAZINAMIDE™, and/or ETHAMBUTOL™ to prophylactically treat or prevent an opportunistic *Mycobacterium avium* complex infection. In another specific embodiment, Therapeutics of the invention are used in any combination with RIFABUTIN™, CLARITHROMYCIN™, and/or AZITHROMYCIN™ to prophylactically treat or prevent an opportunistic *Mycobacterium tuberculosis* infection. In another specific embodiment, Therapeutics of the invention are used in any combination with GANCICLOVIR™, FOSCARNET™, and/or CIDOFOVIR™ to prophylactically treat or prevent an opportunistic cytomegalovirus infection. In another specific embodiment, Therapeutics of the invention are used in any combination with FLUCONAZOLE™, ITRACONAZOLE™, and/or KETOCONAZOLE™ to prophylactically treat or prevent an opportunistic fungal infection. In another specific embodiment, Therapeutics of the invention are used in any combination

with ACYCLOVIR™ and/or FAMCICOLVIR™ to prophylactically treat or prevent an opportunistic herpes simplex virus type I and/or type II infection. In another specific embodiment, Therapeutics of the invention are used in any combination with PYRIMETHAMINE™ and/or LEUCOVORIN™ to prophylactically treat or prevent an opportunistic *Toxoplasma gondii* infection. In another specific embodiment, Therapeutics of the invention are used in any combination with LEUCOVORIN™ and/or NEUPOGEN™ to prophylactically treat or prevent an opportunistic bacterial infection.

[1048] In a further embodiment, the Therapeutics of the invention are administered in combination with an antibiotic agent. Antibiotic agents that may be administered with the Therapeutics of the invention include, but are not limited to, amoxicillin, beta-lactamases, aminoglycosides, beta-lactam (glycopeptide), beta-lactamases, Clindamycin, chloramphenicol, cephalosporins, ciprofloxacin, erythromycin, fluoroquinolones, macrolides, metronidazole, penicillins, quinolones, rapamycin, rifampin, streptomycin, sulfonamide, tetracyclines, trimethoprim, trimethoprim-sulfamethoxazole, and vancomycin.

[1049] In other embodiments, the Therapeutics of the invention are administered in combination with immunestimulants. Immunostimulants that may be administered in combination with the Therapeutics of the invention include, but are not limited to, levamisole (e.g., ERGAMISOL™), isoprinosine (e.g. INOSIPLEX™), interferons (e.g. interferon alpha), and interleukins (e.g., IL-2).

[1050] In other embodiments, Therapeutics of the invention are administered in combination with immunosuppressive agents. Immunosuppressive agents that may be administered in combination with the Therapeutics of the invention include, but are not limited to, steroids, cyclosporine, cyclosporine analogs, cyclophosphamide methylprednisone, prednisone, azathioprine, FK-506, 15-deoxyspergualin, and other immunosuppressive agents that act by suppressing the function of responding T cells. Other immunosuppressive agents that may be administered in combination with the Therapeutics of the invention include, but are not limited to, prednisolone, methotrexate, thalidomide, methoxsalen, rapamycin, leflunomide, mizoribine (BREDININ™), brequinar, deoxyspergualin, and azaspirane (SKF 105685), ORTHOCLONE OKT® 3 (muromonab-CD3), SANDIMMUNE™, NEORAL™, SANGDYA™ (cyclosporine), PROGRAF® (FK506, tacrolimus), CELLCEPT® (mycophenolate motefil, of which the active metabolite is mycophenolic acid), IMURAN™ (azathioprine), glucocorticosteroids, adrenocortical steroids

such as DELTASONE™ (prednisone) and HYDELTRASOL™ (prednisolone), FOLEX™ and MEXATE™ (methotrxate), OXSORALEN-ULTRA™ (methoxsalen) and RAPAMUNE™ (sirolimus). In a specific embodiment, immunosuppressants may be used to prevent rejection of organ or bone marrow transplantation.

[1051] In an additional embodiment, Therapeutics of the invention are administered alone or in combination with one or more intravenous immune globulin preparations. Intravenous immune globulin preparations that may be administered with the Therapeutics of the invention include, but not limited to, GAMMAR™, IVEEGAM™, SANDOGLOBULIN™, GAMMAGARD S/D™, ATGAM™ (antithymocyte glubulin), and GAMIMUNE™. In a specific embodiment, Therapeutics of the invention are administered in combination with intravenous immune globulin preparations in transplantation therapy (e.g., bone marrow transplant).

[1052] In certain embodiments, the Therapeutics of the invention are administered alone or in combination with an anti-inflammatory agent. Anti-inflammatory agents that may be administered with the Therapeutics of the invention include, but are not limited to, corticosteroids (e.g. betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, and triamcinolone), nonsteroidal anti-inflammatory drugs (e.g., diclofenac, diflunisal, etodolac, fenoprofen, floctafenine, flurbiprofen, ibuprofen, indomethacin, ketoprofen, meclofenamate, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, phenylbutazone, piroxicam, sulindac, tenoxicam, tiaprofenic acid, and tolmetin.), as well as antihistamines, aminoarylcarboxylic acid derivatives, arylacetic acid derivatives, arylbutyric acid derivatives, arylcarboxylic acids, arylpropionic acid derivatives, pyrazoles, pyrazolones, salicylic acid derivatives, thiazinecarboxamides, e-acetamidocaproic acid, S-adenosylmethionine, 3-amino-4-hydroxybutyric acid, amixetrine, bendazac, benzydamine, bucolome, difenpiramide, ditazol, emorfazone, guaiazulene, nabumetone, nimesulide, orgotein, oxaceprol, paranyline, perisoxal, pifoxime, proquazone, proxazole, and tenidap.

[1053] In an additional embodiment, the compositions of the invention are administered alone or in combination with an anti-angiogenic agent. Anti-angiogenic agents that may be administered with the compositions of the invention include, but are not limited to, Angiostatin (Entremed, Rockville, MD), Troponin-1 (Boston Life Sciences, Boston, MA), anti-Invasive Factor, retinoic acid and derivatives thereof, paclitaxel (Taxol), Suramin, Tissue

Inhibitor of Metalloproteinase-1, Tissue Inhibitor of Metalloproteinase-2, VEGI, Plasminogen Activator Inhibitor-1, Plasminogen Activator Inhibitor-2, and various forms of the lighter "d group" transition metals.

[1054] Lighter "d group" transition metals include, for example, vanadium, molybdenum, tungsten, titanium, niobium, and tantalum species. Such transition metal species may form transition metal complexes. Suitable complexes of the above-mentioned transition metal species include oxo transition metal complexes.

[1055] Representative examples of vanadium complexes include oxo vanadium complexes such as vanadate and vanadyl complexes. Suitable vanadate complexes include metavanadate and orthovanadate complexes such as, for example, ammonium metavanadate, sodium metavanadate, and sodium orthovanadate. Suitable vanadyl complexes include, for example, vanadyl acetylacetonate and vanadyl sulfate including vanadyl sulfate hydrates such as vanadyl sulfate mono- and trihydrates.

[1056] Representative examples of tungsten and molybdenum complexes also include oxo complexes. Suitable oxo tungsten complexes include tungstate and tungsten oxide complexes. Suitable tungstate complexes include ammonium tungstate, calcium tungstate, sodium tungstate dihydrate, and tungstic acid. Suitable tungsten oxides include tungsten (IV) oxide and tungsten (VI) oxide. Suitable oxo molybdenum complexes include molybdate, molybdenum oxide, and molybdenyl complexes. Suitable molybdate complexes include ammonium molybdate and its hydrates, sodium molybdate and its hydrates, and potassium molybdate and its hydrates. Suitable molybdenum oxides include molybdenum (VI) oxide, molybdenum (VI) oxide, and molybdic acid. Suitable molybdenyl complexes include, for example, molybdenyl acetylacetonate. Other suitable tungsten and molybdenum complexes include hydroxo derivatives derived from, for example, glycerol, tartaric acid, and sugars.

[1057] A wide variety of other anti-angiogenic factors may also be utilized within the context of the present invention. Representative examples include, but are not limited to, platelet factor 4; protamine sulphate; sulphated chitin derivatives (prepared from queen crab shells), (Murata et al., Cancer Res. 51:22-26, (1991)); Sulphated Polysaccharide Peptidoglycan Complex (SP- PG) (the function of this compound may be enhanced by the presence of steroids such as estrogen, and tamoxifen citrate); Staurosporine; modulators of matrix metabolism, including for example, proline analogs, cishydroxyproline, d,L-3,4-dehydroproline, Thiaproline, alpha,alpha-dipyridyl, aminopropionitrile fumarate; 4-propyl-5-

(4-pyridinyl)-2(3H)-oxazolone; Methotrexate; Mitoxantrone; Heparin; Interferons; 2 Macroglobulin-serum; ChIMP-3 (Pavloff et al., J. Bio. Chem. 267:17321-17326, (1992)); Chymostatin (Tomkinson et al., Biochem J. 286:475-480, (1992)); Cyclodextrin Tetradecasulfate; Eponemycin; Camptothecin; Fumagillin (Ingber et al., Nature 348:555-557, (1990)); Gold Sodium Thiomalate ("GST"; Matsubara and Ziff, J. Clin. Invest. 79:1440-1446, (1987)); anticollagenase-serum; alpha2-antiplasmin (Holmes et al., J. Biol. Chem. 262(4):1659-1664, (1987)); Bisantrene (National Cancer Institute); Lobenzarit disodium (N-(2)-carboxyphenyl-4- chloroanthronilic acid disodium or "CCA"; (Takeuchi et al., Agents Actions 36:312-316, (1992)); and metalloproteinase inhibitors such as BB94.

[1058] Additional anti-angiogenic factors that may also be utilized within the context of the present invention include Thalidomide, (Celgene, Warren, NJ); Angiostatic steroid; AGM-1470 (H. Brem and J. Folkman *J Pediatr. Surg.* 28:445-51 (1993)); an integrin alpha v beta 3 antagonist (C. Storgard et al., *J Clin. Invest.* 103:47-54 (1999)); carboxynaminolmidazole; Carboxyamidotriazole (CAI) (National Cancer Institute, Bethesda, MD); Conbretastatin A-4 (CA4P) (OXiGENE, Boston, MA); Squalamine (Magainin Pharmaceuticals, Plymouth Meeting, PA); TNP-470, (Tap Pharmaceuticals, Deerfield, IL); ZD-0101 AstraZeneca (London, UK); APRA (CT2584); Benefin, Byrostatin-1 (SC339555); CGP-41251 (PKC 412); CM101; Dexrazoxane (ICRF187); DMXAA; Endostatin; Flavopridiol; Genestein; GTE; ImmTher; Iressa (ZD1839); Octreotide (Somatostatin); Panretin; Penacillamine; Photopoint; PI-88; Prinomastat (AG-3340) Purlytin; Suradista (FCE26644); Tamoxifen (Nolvadex); Tazarotene; Tetrathiomolybdate; Xeloda (Capecitabine); and 5-Fluorouracil.

[1059] Anti-angiogenic agents that may be administed in combination with the compounds of the invention may work through a variety of mechanisms including, but not limited to, inhibiting proteolysis of the extracellular matrix, blocking the function of endothelial cell-extracellular matrix adhesion molecules, by antagonizing the function of angiogenesis inducers such as growth factors, and inhibiting integrin receptors expressed on proliferating endothelial cells. Examples of anti-angiogenic inhibitors that interfere with extracellular matrix proteolysis and which may be administered in combination with the compositons of the invention include, but are not lmited to, AG-3340 (Agouron, La Jolla, CA), BAY-12-9566 (Bayer, West Haven, CT), BMS-275291 (Bristol Myers Squibb, Princeton, NJ), CGS-27032A (Novartis, East Hanover, NJ), Marimastat (British Biotech,

Oxford, UK), and Metastat (Aeterna, St-Foy, Quebec). Examples of anti-angiogenic inhibitors that act by blocking the function of endothelial cell-extracellular matrix adhesion molecules and which may be administered in combination with the compositons of the invention include, but are not lmited to, EMD-121974 (Merck KcgaA Darmstadt, Germany) and Vitaxin (Ixsys, La Jolla, CA/Medimmune, Gaithersburg, MD). Examples of anti-angiogenic agents that act by directly antagonizing or inhibiting angiogenesis inducers and which may be administered in combination with the compositons of the invention include, but are not lmited to, Angiozyme (Ribozyme, Boulder, CO), Anti-VEGF antibody (Genentech, S. San Francisco, CA), PTK-787/ZK-225846 (Novartis, Basel, Switzerland), SU-101 (Sugen, S. San Francisco, CA), SU-5416 (Sugen/ Pharmacia Upjohn, Bridgewater, NJ), and SU-6668 (Sugen). Other anti-angiogenic agents act to indirectly inhibit angiogenesis. Examples of indirect inhibitors of angiogenesis which may be administered in combination with the compositons of the invention include, but are not limited to, IM-862 (Cytran, Kirkland, WA), Interferon-alpha, IL-12 (Roche, Nutley, NJ), and Pentosan polysulfate (Georgetown University, Washington, DC).

[1060] In particular embodiments, the use of compositions of the invention in combination with anti-angiogenic agents is contemplated for the treatment, prevention, and/or amelioration of an autoimmune disease, such as for example, an autoimmune disease described herein.

[1061] In a particular embodiment, the use of compositions of the invention in combination with anti-angiogenic agents is contemplated for the treatment, prevention, and/or amelioration of arthritis. In a more particular embodiment, the use of compositions of the invention in combination with anti-angiogenic agents is contemplated for the treatment, prevention, and/or amelioration of rheumatoid arthritis.

[1062] In another embodiment, the polynucleotides encoding a polypeptide of the present invention are administered in combination with an angiogenic protein, or polynucleotides encoding an angiogenic protein. Examples of angiogenic proteins that may be administered with the compositions of the invention include, but are not limited to, acidic and basic fibroblast growth factors, VEGF-1, VEGF-2, VEGF-3, epidermal growth factor alpha and beta, platelet-derived endothelial cell growth factor, platelet-derived growth factor, tumor necrosis factor alpha, hepatocyte growth factor, insulin-like growth factor, colony stimulating

factor, macrophage colony stimulating factor, granulocyte/macrophage colony stimulating factor, and nitric oxide synthase.

[1063] In additional embodiments, compositions of the invention are administered in combination with a chemotherapeutic agent. Chemotherapeutic agents that may be administered with the Therapeutics of the invention include, but are not limited to alkylating agents such as nitrogen mustards (for example, Mechlorethamine, cyclophosphamide, Cyclophosphamide Ifosfamide, Melphalan (L-sarcolysin), and Chlorambucil), ethylenimines and methylmelamines (for example, Hexamethylmelamine and Thiotepa), alkyl sulfonates (for example, Busulfan), nitrosoureas (for example, Carmustine (BCNU), Lomustine (CCNU), Semustine (methyl-CCNU), and Streptozocin (streptozotocin)), triazenes (for example, Dacarbazine (DTIC; dimethyltriazenoimidazolecarboxamide)), folic acid analogs (for example, Methotrexate (amethopterin)), pyrimidine analogs (for example, Fluorouacil (5-fluorouracil; 5-FU), Floxuridine (fluorodeoxyuridine; FudR), and Cytarabine (cytosine arabinoside)), purine analogs and related inhibitors (for example, Mercaptopurine (6-mercaptopurine; 6-MP), Thioguanine (6-thioguanine; TG), and Pentostatin (2'-deoxycoformycin)), vinca alkaloids (for example, Vinblastine (VLB, vinblastine sulfate)) and Vincristine (vincristine sulfate)), epipodophyllotoxins (for example, Etoposide and Teniposide), antibiotics (for example, Dactinomycin (actinomycin D), Daunorubicin (daunomycin; rubidomycin), Doxorubicin, Bleomycin, Plicamycin (mithramycin), and Mitomycin (mitomycin C), enzymes (for example, L-Asparaginase), biological response modifiers (for example, Interferon-alpha and interferon-alpha-2b), platinum coordination compounds (for example, Cisplatin (cis-DDP) and Carboplatin), anthracenedione (Mitoxantrone), substituted ureas (for example, Hydroxyurea), methylhydrazine derivatives (for example, Procarbazine (N-methylhydrazine; MIH), adrenocorticosteroids (for example, Prednisone), progestins (for example, Hydroxyprogesterone caproate, Medroxyprogesterone, Medroxyprogesterone acetate, and Megestrol acetate), estrogens (for example, Diethylstilbestrol (DES), Diethylstilbestrol diphosphate, Estradiol, and Ethinyl estradiol), antiestrogens (for example, Tamoxifen), androgens (Testosterone proprionate, and Fluoxymesterone), antiandrogens (for example, Flutamide), gonadotropin-releasing horomone analogs (for example, Leuprolide), other hormones and hormone analogs (for example, methyltestosterone, estramustine, estramustine phosphate sodium, chlorotrianisene, and testolactone), and others (for example, dicarbazine, glutamic acid, and mitotane).

[1064] In one embodiment, the compositions of the invention are administered in combination with one or more of the following drugs: infliximab (also known as Remicade™ Centocor, Inc.), Trocade (Roche, RO-32-3555), Leflunomide (also known as Arava™ from Hoechst Marion Roussel), Kineret™ (an IL-1 Receptor antagonist also known as Anakinra from Amgen, Inc.)

[1065] In a specific embodiment, compositions of the invention are administered in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or combination of one or more of the components of CHOP. In one embodiment, the compositions of the invention are administered in combination with anti-CD20 antibodies, human monoclonal anti-CD20 antibodies. In another embodiment, the compositions of the invention are administered in combination with anti-CD20 antibodies and CHOP, or anti-CD20 antibodies and any combination of one or more of the components of CHOP, particularly cyclophosphamide and/or prednisone. In a specific embodiment, compositions of the invention are administered in combination with Rituximab. In a further embodiment, compositions of the invention are administered with Rituximab and CHOP, or Rituximab and any combination of one or more of the components of CHOP, particularly cyclophosphamide and/or prednisone. In a specific embodiment, compositions of the invention are administered in combination with tositumomab. In a further embodiment, compositions of the invention are administered with tositumomab and CHOP, or tositumomab and any combination of one or more of the components of CHOP, particularly cyclophosphamide and/or prednisone. The anti-CD20 antibodies may optionally be associated with radioisotopes, toxins or cytotoxic prodrugs.

[1066] In another specific embodiment, the compositions of the invention are administered in combination Zevalin™. In a further embodiment, compositions of the invention are administered with Zevalin™ and CHOP, or Zevalin™ and any combination of one or more of the components of CHOP, particularly cyclophosphamide and/or prednisone. Zevalin™ may be associated with one or more radisotopes. Particularly preferred isotopes are ^{90}Y and ^{111}In.

[1067] In an additional embodiment, the Therapeutics of the invention are administered in combination with cytokines. Cytokines that may be administered with the Therapeutics of the invention include, but are not limited to, IL2, IL3, IL4, IL5, IL6, IL7, IL10, IL12, IL13, IL15, anti-CD40, CD40L, IFN-gamma and TNF-alpha. In another embodiment,

Therapeutics of the invention may be administered with any interleukin, including, but not limited to, IL-1alpha, IL-1beta, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IL-16, IL-17, IL-18, IL-19, IL-20, and IL-21.

[1068] In one embodiment, the Therapeutics of the invention are administered in combination with members of the TNF family. TNF, TNF-related or TNF-like molecules that may be administered with the Therapeutics of the invention include, but are not limited to, soluble forms of TNF-alpha, lymphotoxin-alpha (LT-alpha, also known as TNF-beta), LT-beta (found in complex heterotrimer LT-alpha2-beta), OPGL, FasL, CD27L, CD30L, CD40L, 4-1BBL, DcR3, OX40L, TNF-gamma (International Publication No. WO 96/14328), AIM-I (International Publication No. WO 97/33899), endokine-alpha (International Publication No. WO 98/07880), OPG, and neutrokine-alpha (International Publication No. WO 98/18921, OX40, and nerve growth factor (NGF), and soluble forms of Fas, CD30, CD27, CD40 and 4-IBB, TR2 (International Publication No. WO 96/34095), DR3 (International Publication No. WO 97/33904), DR4 (International Publication No. WO 98/32856), TR5 (International Publication No. WO 98/30693), TRANK, TR9 (International Publication No. WO 98/56892),TR10 (International Publication No. WO 98/54202), 312C2 (International Publication No. WO 98/06842), and TR12, and soluble forms CD154, CD70, and CD153.

[1069] In an additional embodiment, the Therapeutics of the invention are administered in combination with angiogenic proteins. Angiogenic proteins that may be administered with the Therapeutics of the invention include, but are not limited to, Glioma Derived Growth Factor (GDGF), as disclosed in European Patent Number EP-399816; Platelet Derived Growth Factor-A (PDGF-A), as disclosed in European Patent Number EP-682110; Platelet Derived Growth Factor-B (PDGF-B), as disclosed in European Patent Number EP-282317; Placental Growth Factor (PlGF), as disclosed in International Publication Number WO 92/06194; Placental Growth Factor-2 (PlGF-2), as disclosed in Hauser et al., Growth Factors, 4:259-268 (1993); Vascular Endothelial Growth Factor (VEGF), as disclosed in International Publication Number WO 90/13649; Vascular Endothelial Growth Factor-A (VEGF-A), as disclosed in European Patent Number EP-506477; Vascular Endothelial Growth Factor-2 (VEGF-2), as disclosed in International Publication Number WO 96/39515; Vascular Endothelial Growth Factor B (VEGF-3); Vascular Endothelial Growth Factor B-186 (VEGF-B186), as disclosed in International Publication Number WO 96/26736; Vascular Endothelial

Growth Factor-D (VEGF-D), as disclosed in International Publication Number WO 98/02543; Vascular Endothelial Growth Factor-D (VEGF-D), as disclosed in International Publication Number WO 98/07832; and Vascular Endothelial Growth Factor-E (VEGF-E), as disclosed in German Patent Number DE19639601. The above mentioned references are herein incorporated by reference in their entireties.

[1070] In an additional embodiment, the Therapeutics of the invention are administered in combination with Fibroblast Growth Factors. Fibroblast Growth Factors that may be administered with the Therapeutics of the invention include, but are not limited to, FGF-1, FGF-2, FGF-3, FGF-4, FGF-5, FGF-6, FGF-7, FGF-8, FGF-9, FGF-10, FGF-11, FGF-12, FGF-13, FGF-14, and FGF-15.

[1071] In an additional embodiment, the Therapeutics of the invention are administered in combination with hematopoietic growth factors. Hematopoietic growth factors that may be administered with the Therapeutics of the invention include, but are not limited to, granulocyte macrophage colony stimulating factor (GM-CSF) (sargramostim, LEUKINE™, PROKINE™), granulocyte colony stimulating factor (G-CSF) (filgrastim, NEUPOGEN™), macrophage colony stimulating factor (M-CSF, CSF-1) erythropoietin (epoetin alfa, EPOGEN™, PROCRIT™), stem cell factor (SCF, c-kit ligand, steel factor), megakaryocyte colony stimulating factor, PIXY321 (a GMCSF/IL-3 fusion protein), interleukins, especially any one or more of IL-1 through IL-12, interferon-gamma, or thrombopoietin.

[1072] In certain embodiments, Therapeutics of the present invention are administered in combination with adrenergic blockers, such as, for example, acebutolol, atenolol, betaxolol, bisoprolol, carteolol, labetalol, metoprolol, nadolol, oxprenolol, penbutolol, pindolol, propranolol, sotalol, and timolol.

[1073] In another embodiment, the Therapeutics of the invention are administered in combination with an antiarrhythmic drug (e.g., adenosine, amidoarone, bretylium, digitalis, digoxin, digitoxin, diliazem, disopyramide, esmolol, flecainide, lidocaine, mexiletine, moricizine, phenytoin, procainamide, N-acetyl procainamide, propafenone, propranolol, quinidine, sotalol, tocainide, and verapamil).

[1074] In another embodiment, the Therapeutics of the invention are administered in combination with diuretic agents, such as carbonic anhydrase-inhibiting agents (e.g., acetazolamide, dichlorphenamide, and methazolamide), osmotic diuretics (e.g., glycerin, isosorbide, mannitol, and urea), diuretics that inhibit Na^{+}-K^{+}-$2Cl^{-}$ symport (e.g., furosemide,

bumetanide, azosemide, piretanide, tripamide, ethacrynic acid, muzolimine, and torsemide), thiazide and thiazide-like diuretics (e.g., bendroflumethiazide, benzthiazide, chlorothiazide, hydrochlorothiazide, hydroflumethiazide, methyclothiazide, polythiazide, trichormethiazide, chlorthalidone, indapamide, metolazone, and quinethazone), potassium sparing diuretics (e.g., amiloride and triamterene), and mineralcorticoid receptor antagonists (e.g., spironolactone, canrenone, and potassium canrenoate).

[1075] In one embodiment, the Therapeutics of the invention are administered in combination with treatments for endocrine and/or hormone imbalance disorders. Treatments for endocrine and/or hormone imbalance disorders include, but are not limited to, ^{127}I, radioactive isotopes of iodine such as ^{131}I and ^{123}I; recombinant growth hormone, such as HUMATROPE™ (recombinant somatropin); growth hormone analogs such as PROTROPIN™ (somatrem); dopamine agonists such as PARLODEL™ (bromocriptine); somatostatin analogs such as SANDOSTATIN™ (octreotide); gonadotropin preparations such as PREGNYL™, A.P.L.™ and PROFASI™ (chorionic gonadotropin (CG)), PERGONAL™ (menotropins), and METRODIN™ (urofollitropin (uFSH)); synthetic human gonadotropin releasing hormone preparations such as FACTREL™ and LUTREPULSE™ (gonadorelin hydrochloride); synthetic gonadotropin agonists such as LUPRON™ (leuprolide acetate), SUPPRELIN™ (histrelin acetate), SYNAREL™ (nafarelin acetate), and ZOLADEX™ (goserelin acetate); synthetic preparations of thyrotropin-releasing hormone such as RELEFACT TRH™ and THYPINONE™ (protirelin); recombinant human TSH such as THYROGEN™; synthetic preparations of the sodium salts of the natural isomers of thyroid hormones such as L-T_4™, SYNTHROID™ and LEVOTHROID™ (levothyroxine sodium), L-T_3™, CYTOMEL™ and TRIOSTAT™ (liothyroine sodium), and THYROLAR™ (liotrix); antithyroid compounds such as 6-*n*-propylthiouracil (propylthiouracil), 1-methyl-2-mercaptoimidazole and TAPAZOLE™ (methimazole), NEO-MERCAZOLE™ (carbimazole); beta-adrenergic receptor antagonists such as propranolol and esmolol; Ca^{2+} channel blockers; dexamethasone and iodinated radiological contrast agents such as TELEPAQUE™ (iopanoic acid) and ORAGRAFIN™ (sodium ipodate).

[1076] Additional treatments for endocrine and/or hormone imbalance disorders include, but are not limited to, estrogens or congugated estrogens such as ESTRACE™ (estradiol), ESTINYL™ (ethinyl estradiol), PREMARIN™, ESTRATAB™, ORTHO-EST™, OGEN™

and estropipate (estrone), ESTROVIS™ (quinestrol), ESTRADERM™ (estradiol), DELESTROGEN™ and VALERGEN™ (estradiol valerate), DEPO-ESTRADIOL CYPIONATE™ and ESTROJECT LA™ (estradiol cypionate); antiestrogens such as NOLVADEX™ (tamoxifen), SEROPHENE™ and CLOMID™ (clomiphene); progestins such as DURALUTIN™ (hydroxyprogesterone caproate), MPA™ and DEPO-PROVERA™ (medroxyprogesterone acetate), PROVERA™ and CYCRIN™ (MPA), MEGACE™ (megestrol acetate), NORLUTIN™ (norethindrone), and NORLUTATE™ and AYGESTIN™ (norethindrone acetate); progesterone implants such as NORPLANT SYSTEM™ (subdermal implants of norgestrel); antiprogestins such as RU 486™ (mifepristone); hormonal contraceptives such as ENOVID™ (norethynodrel plus mestranol), PROGESTASERT™ (intrauterine device that releases progesterone), LOESTRIN™, BREVICON™, MODICON™, GENORA™, NELONA™, NORINYL™, OVACON-35™ and OVACON-50™ (ethinyl estradiol/norethindrone), LEVLEN™, NORDETTE™, TRI-LEVLEN™ and TRIPHASIL-21™ (ethinyl estradiol/levonorgestrel) LO/OVRAL™ and OVRAL™ (ethinyl estradiol/norgestrel), DEMULEN™ (ethinyl estradiol/ethynodiol diacetate), NORINYL™, ORTHO-NOVUM™, NORETHIN™, GENORA™, and NELOVA™ (norethindrone/mestranol), DESOGEN™ and ORTHO-CEPT™ (ethinyl estradiol/desogestrel), ORTHO-CYCLEN™ and ORTHO-TRICYCLEN™ (ethinyl estradiol/norgestimate), MICRONOR™ and NOR-QD™ (norethindrone), and OVRETTE™ (norgestrel).

[1077] Additional treatments for endocrine and/or hormone imbalance disorders include, but are not limited to, testosterone esters such as methenolone acetate and testosterone undecanoate; parenteral and oral androgens such as TESTOJECT-50™ (testosterone), TESTEX™ (testosterone propionate), DELATESTRYL™ (testosterone enanthate), DEPO-TESTOSTERONE™ (testosterone cypionate), DANOCRINE™ (danazol), HALOTESTIN™ (fluoxymesterone), ORETON METHYL™, TESTRED™ and VIRILON™ (methyltestosterone), and OXANDRIN™ (oxandrolone); testosterone transdermal systems such as TESTODERM™; androgen receptor antagonist and 5-alpha-reductase inhibitors such as ANDROCUR™ (cyproterone acetate), EULEXIN™ (flutamide), and PROSCAR™ (finasteride); adrenocorticotropic hormone preparations such as CORTROSYN™

(cosyntropin); adrenocortical steroids and their synthetic analogs such as ACLOVATE™ (alclometasone dipropionate), CYCLOCORT™ (amcinonide), BECLOVENT™ and VANCERIL™ (beclomethasone dipropionate), CELESTONE™ (betamethasone), BENISONE™ and UTICORT™ (betamethasone benzoate), DIPROSONE™ (betamethasone dipropionate), CELESTONE PHOSPHATE™ (betamethasone sodium phosphate), CELESTONE SOLUSPAN™ (betamethasone sodium phosphate and acetate), BETA-VAL™ and VALISONE™ (betamethasone valerate), TEMOVATE™ (clobetasol propionate), CLODERM™ (clocortolone pivalate), CORTEF™ and HYDROCORTONE™ (cortisol (hydrocortisone)), HYDROCORTONE ACETATE™ (cortisol (hydrocortisone) acetate), LOCOID™ (cortisol (hydrocortisone) butyrate), HYDROCORTONE PHOSPHATE™ (cortisol (hydrocortisone) sodium phosphate), A-HYDROCORT™ and SOLU CORTEF™ (cortisol (hydrocortisone) sodium succinate), WESTCORT™ (cortisol (hydrocortisone) valerate), CORTISONE ACETATE™ (cortisone acetate), DESOWEN™ and TRIDESILON™ (desonide), TOPICORT™ (desoximetasone), DECADRON™ (dexamethasone), DECADRON LA™ (dexamethasone acetate), DECADRON PHOSPHATE™ and HEXADROL PHOSPHATE™ (dexamethasone sodium phosphate), FLORONE™ and MAXIFLOR™ (diflorasone diacetate), FLORINEF ACETATE™ (fludrocortisone acetate), AEROBID™ and NASALIDE™ (flunisolide), FLUONID™ and SYNALAR™ (fluocinolone acetonide), LIDEX™ (fluocinonide), FLUOR-OP™ and FML™ (fluorometholone), CORDRAN™ (flurandrenolide), HALOG™ (halcinonide), HMS LIZUIFILM™ (medrysone), MEDROL™ (methylprednisolone), DEPO-MEDROL™ and MEDROL ACETATE™ (methylprednisone acetate), A-METHAPRED™ and SOLUMEDROL™ (methylprednisolone sodium succinate), ELOCON™ (mometasone furoate), HALDRONE™ (paramethasone acetate), DELTA-CORTEF™ (prednisolone), ECONOPRED™ (prednisolone acetate), HYDELTRASOL™ (prednisolone sodium phosphate), HYDELTRA-T.B.A™ (prednisolone tebutate), DELTASONE™ (prednisone), ARISTOCORT™ and KENACORT™ (triamcinolone), KENALOG™ (triamcinolone acetonide), ARISTOCORT™ and KENACORT DIACETATE™ (triamcinolone diacetate), and ARISTOSPAN™ (triamcinolone hexacetonide); inhibitors of biosynthesis and action of

adrenocortical steroids such as CYTADREN™ (aminoglutethimide), NIZORAL™ (ketoconazole), MODRASTANE™ (trilostane), and METOPIRONE™ (metyrapone);

[1078] Additional treatments for endocrine and/or hormone imbalance disorders include, but are not limited to bovine, porcine or human insulin or mixtures thereof; insulin analogs; recombinant human insulin such as HUMULIN™ and NOVOLIN™; oral hypoglycemic agents such as ORAMIDE™ and ORINASE™ (tolbutamide), DIABINESE™ (chlorpropamide), TOLAMIDE™ and TOLINASE™ (tolazamide), DYMELOR™ (acetohexamide), glibenclamide, MICRONASE™, DIBETA™ and GLYNASE™ (glyburide), GLUCOTROL™ (glipizide), and DIAMICRON™ (gliclazide), GLUCOPHAGE™ (metformin), PRECOSE™ (acarbose), AMARYL™ (glimepiride), and ciglitazone; thiazolidinediones (TZDs) such as rosiglitazone, AVANDIA™ (rosiglitazone maleate) ACTOS™ (piogliatazone), and troglitazone; alpha-glucosidase inhibitors; bovine or porcine glucagon; somatostatins such as SANDOSTATIN™ (octreotide); and diazoxides such as PROGLYCEM™ (diazoxide). In still other embodiments, Therapeutics of the invention are administered in combination with one or more of the following: a biguanide antidiabetic agent, a glitazone antidiabetic agent, and a sulfonylurea antidiabetic agent.

[1079] In one embodiment, the Therapeutics of the invention are administered in combination with treatments for uterine motility disorders. Treatments for uterine motility disorders include, but are not limited to, estrogen drugs such as conjugated estrogens (e.g., PREMARIN® and ESTRATAB®), estradiols (e.g., CLIMARA® and ALORA®), estropipate, and chlorotrianisene; progestin drugs (e.g., AMEN® (medroxyprogesterone), MICRONOR® (norethidrone acetate), PROMETRIUM® progesterone, and megestrol acetate); and estrogen/progesterone combination therapies such as, for example, conjugated estrogens/medroxyprogesterone (e.g., PREMPRO™ and PREMPHASE®) and norethindrone acetate/ethinyl estsradiol (e.g., FEMHRT™).

[1080] In an additional embodiment, the Therapeutics of the invention are administered in combination with drugs effective in treating iron deficiency and hypochromic anemias, including but not limited to, ferrous sulfate (iron sulfate, FEOSOL™), ferrous fumarate (e.g., FEOSTAT™), ferrous gluconate (e.g., FERGON™), polysaccharide-iron complex (e.g., NIFEREX™), iron dextran injection (e.g., INFED™), cupric sulfate, pyroxidine, riboflavin, Vitamin B_{12}, cyancobalamin injection (e.g., REDISOL™, RUBRAMIN PC™),

hydroxocobalamin, folic acid (e.g., FOLVITE™), leucovorin (folinic acid, 5-CHOH4PteGlu, citrovorum factor) or WELLCOVORIN (Calcium salt of leucovorin), transferrin or ferritin.

[1081] In certain embodiments, the Therapeutics of the invention are administered in combination with agents used to treat psychiatric disorders. Psychiatric drugs that may be administered with the Therapeutics of the invention include, but are not limited to, antipsychotic agents (e.g., chlorpromazine, chlorprothixene, clozapine, fluphenazine, haloperidol, loxapine, mesoridazine, molindone, olanzapine, perphenazine, pimozide, quetiapine, risperidone, thioridazine, thiothixene, trifluoperazine, and triflupromazine), antimanic agents (e.g., carbamazepine, divalproex sodium, lithium carbonate, and lithium citrate), antidepressants (e.g., amitriptyline, amoxapine, bupropion, citalopram, clomipramine, desipramine, doxepin, fluvoxamine, fluoxetine, imipramine, isocarboxazid, maprotiline, mirtazapine, nefazodone, nortriptyline, paroxetine, phenelzine, protriptyline, sertraline, tranylcypromine, trazodone, trimipramine, and venlafaxine), antianxiety agents (e.g., alprazolam, buspirone, chlordiazepoxide, clorazepate, diazepam, halazepam, lorazepam, oxazepam, and prazepam), and stimulants (e.g., d-amphetamine, methylphenidate, and pemoline).

[1082] In other embodiments, the Therapeutics of the invention are administered in combination with agents used to treat neurological disorders. Neurological agents that may be administered with the Therapeutics of the invention include, but are not limited to, antiepileptic agents (e.g., carbamazepine, clonazepam, ethosuximide, phenobarbital, phenytoin, primidone, valproic acid, divalproex sodium, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, zonisamide, diazepam, lorazepam, and clonazepam), antiparkinsonian agents (e.g., levodopa/carbidopa, selegiline, amantidine, bromocriptine, pergolide, ropinirole, pramipexole, benztropine; biperiden; ethopropazine; procyclidine; trihexyphenidyl, tolcapone), and ALS therapeutics (e.g. riluzole).

[1083] In another embodiment, Therapeutics of the invention are administered in combination with vasodilating agents and/or calcium channel blocking agents. Vasodilating agents that may be administered with the Therapeutics of the invention include, but are not limited to, Angiotensin Converting Enzyme (ACE) inhibitors (e.g., papaverine, isoxsuprine, benazepril, captopril, cilazapril, enalapril, enalaprilat, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, spirapril, trandolapril, and nylidrin), and nitrates (e.g., isosorbide dinitrate, isosorbide mononitrate, and nitroglycerin). Examples of calcium channel

blocking agents that may be administered in combination with the Therapeutics of the invention include, but are not limited to amlodipine, bepridil, diltiazem, felodipine, flunarizine, isradipine, nicardipine, nifedipine, nimodipine, and verapamil.

[1084] In certain embodiments, the Therapeutics of the invention are administered in combination with treatments for gastrointestinal disorders. Treatments for gastrointestinal disorders that may be administered with the Therapeutic of the invention include, but are not limited to, H_2 histamine receptor antagonists (e.g., TAGAMET™ (cimetidine), ZANTAC™ (ranitidine), PEPCID™ (famotidine), and AXID™ (nizatidine)); inhibitors of H^+, K^+ ATPase (e.g., PREVACID™ (lansoprazole) and PRILOSEC™ (omeprazole)); Bismuth compounds (e.g., PEPTO-BISMOL™ (bismuth subsalicylate) and DE-NOL™ (bismuth subcitrate)); various antacids; sucralfate; prostaglandin analogs (e.g. CYTOTEC™ (misoprostol)); muscarinic cholinergic antagonists; laxatives (e.g., surfactant laxatives, stimulant laxatives, saline and osmotic laxatives); antidiarrheal agents (e.g., LOMOTIL™ (diphenoxylate), MOTOFEN™ (diphenoxin), and IMODIUM™ (loperamide hydrochloride)), synthetic analogs of somatostatin such as SANDOSTATIN™ (octreotide), antiemetic agents (e.g., ZOFRAN™ (ondansetron), KYTRIL™ (granisetron hydrochloride), tropisetron, dolasetron, metoclopramide, chlorpromazine, perphenazine, prochlorperazine, promethazine, thiethylperazine, triflupromazine, domperidone, haloperidol, droperidol, trimethobenzamide, dexamethasone, methylprednisolone, dronabinol, and nabilone); D2 antagonists (e.g., metoclopramide, trimethobenzamide and chlorpromazine); bile salts; chenodeoxycholic acid; ursodeoxycholic acid; and pancreatic enzyme preparations such as pancreatin and pancrelipase.

[1085] In additional embodiments, the Therapeutics of the invention are administered in combination with other therapeutic or prophylactic regimens, such as, for example, radiation therapy.

Example 11: Method of Treating Decreased Levels of the Polypeptide

[1086] It will be appreciated that conditions caused by a decrease in the standard or normal expression level of a polypeptide in an individual can be treated by administering the polypeptide of the present invention, preferably in the secreted and/or soluble form. Thus, the invention also provides a method of treatment of an individual in need of an increased

level of the polypeptide comprising administering to such an individual a pharmaceutical composition comprising an amount of the polypeptide to increase the activity level of the polypeptide in such an individual.

[1087] For example, a patient with decreased levels of a polypeptide receives a daily dose 0.1-100 ug/kg of the polypeptide for six consecutive days. Preferably, the polypeptide is in the secreted form. The exact details of the dosing scheme, based on administration and formulation, are provided in Example 10.

Example 12: Method of Treating Increased Levels of the Polypeptide

[1088] Antisense technology is used to inhibit production of a polypeptide of the present invention. This technology is one example of a method of decreasing levels of a polypeptide, preferably a secreted form, due to a variety of etiologies, such as cancer.

[1089] For example, a patient diagnosed with abnormally increased levels of a polypeptide is administered intravenously antisense polynucleotides at 0.5, 1.0, 1.5, 2.0 and 3.0 mg/kg day for 21 days. This treatment is repeated after a 7-day rest period if the treatment was well tolerated. The antisense polynucleotides of the present invention can be formulated using techniques and formulations described herein (e.g., see Example 10) or otherwise known in the art.

Example 13: Method of Treatment Using Gene Therapy - Ex Vivo

[1090] One method of gene therapy transplants fibroblasts, which are capable of expressing a polypeptide, onto a patient. Generally, fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in tissue-culture medium and separated into small pieces. Small chunks of the tissue are placed on a wet surface of a tissue culture flask, approximately ten pieces are placed in each flask. The flask is turned upside down, closed tight and left at room temperature over night. After 24 hours at room temperature, the flask is inverted and the chunks of tissue remain fixed to the bottom of the flask and fresh media (e.g., Ham's F12 media, with 10% FBS, penicillin and streptomycin) is added. The flasks are then incubated at 37°C for approximately one week.

[1091] At this time, fresh media is added and subsequently changed every several days. After an additional two weeks in culture, a monolayer of fibroblasts emerge. The monolayer is trypsinized and scaled into larger flasks.

[1092] pMV-7 (Kirschmeier, P.T. et al., DNA, 7:219-25 (1988)), flanked by the long terminal repeats of the Moloney murine sarcoma virus, is digested with EcoRI and HindIII and subsequently treated with calf intestinal phosphatase. The linear vector is fractionated on agarose gel and purified, using glass beads.

[1093] The cDNA encoding a polypeptide of the present invention can be amplified using PCR primers which correspond to the 5' and 3' end sequences respectively as set forth in Example 1 using primers and having appropriate restriction sites and initiation/stop codons, if necessary. Preferably, the 5' primer contains an EcoRI site and the 3' primer includes a HindIII site. Equal quantities of the Moloney murine sarcoma virus linear backbone and the amplified EcoRI and HindIII fragment are added together, in the presence of T4 DNA ligase. The resulting mixture is maintained under conditions appropriate for ligation of the two fragments. The ligation mixture is then used to transform bacteria HB101, which are then plated onto agar containing kanamycin for the purpose of confirming that the vector has the gene of interest properly inserted.

[1094] The amphotropic pA317 or GP+am12 packaging cells are grown in tissue culture to confluent density in Dulbecco's Modified Eagles Medium (DMEM) with 10% calf serum (CS), penicillin and streptomycin. The MSV vector containing the gene is then added to the media and the packaging cells transduced with the vector. The packaging cells now produce infectious viral particles containing the gene (the packaging cells are now referred to as producer cells).

[1095] Fresh media is added to the transduced producer cells, and subsequently, the media is harvested from a 10 cm plate of confluent producer cells. The spent media, containing the infectious viral particles, is filtered through a millipore filter to remove detached producer cells and this media is then used to infect fibroblast cells. Media is removed from a sub-confluent plate of fibroblasts and quickly replaced with the media from the producer cells. This media is removed and replaced with fresh media. If the titer of virus is high, then virtually all fibroblasts will be infected and no selection is required. If the titer is very low, then it is necessary to use a retroviral vector that has a selectable marker, such as neo or his.

Once the fibroblasts have been efficiently infected, the fibroblasts are analyzed to determine whether protein is produced.

[1096] The engineered fibroblasts are then transplanted onto the host, either alone or after having been grown to confluence on cytodex 3 microcarrier beads.

Example 14: Gene Therapy Using Endogenous B7-like Genes

[1097] Another method of gene therapy according to the present invention involves operably associating the endogenous B7-like gene sequence with a promoter via homologous recombination as described, for example, in U.S. Patent NO: 5,641,670, issued June 24, 1997; International Publication NO: WO 96/29411, published September 26, 1996; International Publication NO: WO 94/12650, published August 4, 1994; Koller et al., *Proc. Natl. Acad. Sci. USA,* 86:8932-8935 (1989); and Zijlstra et al., *Nature,* 342:435-438 (1989). This method involves the activation of a gene which is present in the target cells, but which is not expressed in the cells, or is expressed at a lower level than desired.

[1098] Polynucleotide constructs are made which contain a promoter and targeting sequences, which are homologous to the 5' non-coding sequence of the endogenous B7-like gene, flanking the promoter. The targeting sequence will be sufficiently near the 5' end of the B7-like gene so the promoter will be operably linked to the endogenous sequence upon homologous recombination. The promoter and the targeting sequences can be amplified using PCR. Preferably, the amplified promoter contains distinct restriction enzyme sites on the 5' and 3' ends. Preferably, the 3' end of the first targeting sequence contains the same restriction enzyme site as the 5' end of the amplified promoter and the 5' end of the second targeting sequence contains the same restriction site as the 3' end of the amplified promoter.

[1099] The amplified promoter and the amplified targeting sequences are digested with the appropriate restriction enzymes and subsequently treated with calf intestinal phosphatase. The digested promoter and digested targeting sequences are added together in the presence of T4 DNA ligase. The resulting mixture is maintained under conditions appropriate for ligation of the two fragments. The construct is size fractionated on an agarose gel then purified by phenol extraction and ethanol precipitation.

[1100] In this Example, the polynucleotide constructs are administered as naked polynucleotides via electroporation. However, the polynucleotide constructs may also be

administered with transfection-facilitating agents, such as liposomes, viral sequences, viral particles, precipitating agents, etc. Such methods of delivery are known in the art.

[1101] Once the cells are transfected, homologous recombination will take place which results in the promoter being operably linked to the endogenous B7-like gene sequence. This results in the expression of B7-like polypeptides in the cell. Expression may be detected by immunological staining, or any other method known in the art.

[1102] Fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in DMEM + 10% fetal calf serum. Exponentially growing or early stationary phase fibroblasts are trypsinized and rinsed from the plastic surface with nutrient medium. An aliquot of the cell suspension is removed for counting, and the remaining cells are subjected to centrifugation. The supernatant is aspirated and the pellet is resuspended in 5 ml of electroporation buffer (20 mM HEPES pH 7.3, 137 mM NaCl, 5 mM KCl, 0.7 mM Na_2HPO_4, 6 mM dextrose). The cells are recentrifuged, the supernatant aspirated, and the cells resuspended in electroporation buffer containing 1 mg/ml acetylated bovine serum albumin. The final cell suspension contains approximately $3X10^6$ cells/ml. Electroporation should be performed immediately following resuspension.

[1103] Plasmid DNA is prepared according to standard techniques. For example, to construct a plasmid for targeting to the B7-like locus, plasmid pUC18 (MBI Fermentas, Amherst, NY) is digested with HindIII. The CMV promoter is amplified by PCR with an XbaI site on the 5' end and a BamHI site on the 3'end. Two B7-like non-coding gene sequences are amplified via PCR: one B7-like non-coding sequence (B7-like fragment 1) is amplified with a HindIII site at the 5' end and an Xba site at the 3'end; the other B7-like non-coding sequence (B7-like fragment 2) is amplified with a BamHI site at the 5'end and a HindIII site at the 3'end. The CMV promoter and B7-like fragments are digested with the appropriate enzymes (CMV promoter - XbaI and BamHI; B7-like fragment 1 - XbaI; B7-like fragment 2 - BamHI) and ligated together. The resulting ligation product is digested with HindIII, and ligated with the HindIII-digested pUC18 plasmid.

[1104] Plasmid DNA is added to a sterile cuvette with a 0.4 cm electrode gap (Bio-Rad). The final DNA concentration is generally at least 120 μg/ml. 0.5 ml of the cell suspension (containing approximately $1.5.X10^6$ cells) is then added to the cuvette, and the cell suspension and DNA solutions are gently mixed. Electroporation is performed with a Gene-Pulser apparatus (Bio-Rad). Capacitance and voltage are set at 960 μF and 250-300 V,

respectively. As voltage increases, cell survival decreases, but the percentage of surviving cells that stably incorporate the introduced DNA into their genome increases dramatically. Given these parameters, a pulse time of approximately 14-20 mSec should be observed.

[1105] Electroporated cells are maintained at room temperature for approximately 5 min, and the contents of the cuvette are then gently removed with a sterile transfer pipette. The cells are added directly to 10 ml of prewarmed nutrient media (DMEM with 15% calf serum) in a 10 cm dish and incubated at 37 degree C. The following day, the media is aspirated and replaced with 10 ml of fresh media and incubated for a further 16-24 hours.

[1106] The engineered fibroblasts are then injected into the host, either alone or after having been grown to confluence on cytodex 3 microcarrier beads. The fibroblasts now produce the protein product. The fibroblasts can then be introduced into a patient as described above.

Example 15: Method of Treatment Using Gene Therapy - In Vivo

[1107] Another aspect of the present invention is using *in vivo* gene therapy methods to treat disorders, diseases and conditions. The gene therapy method relates to the introduction of naked nucleic acid (DNA, RNA, and antisense DNA or RNA) B7-like sequences into an animal to increase or decrease the expression of the B7-like polypeptide. The B7-like polynucleotide may be operatively linked to a promoter or any other genetic elements necessary for the expression of the B7-like polypeptide by the target tissue. Such gene therapy and delivery techniques and methods are known in the art, see, for example, WO90/11092, WO98/11779; U.S. Patent NO: 5693622, 5705151, 5580859; Tabata et al., *Cardiovasc. Res.* 35(3):470-479 (1997), Chao J et al., *Pharmacol. Res.*, 35(6):517-522 (1997), Wolff, *Neuromuscul. Disord.* 7(5):314-318 (1997), Schwartz et al., *Gene Ther.*, 3(5):405-411 (1996), Tsurumi Y. et al., *Circulation*, 94(12):3281-3290 (1996) (incorporated herein by reference).

[1108] The B7-like polynucleotide constructs may be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, intestine and the like). The B7-like polynucleotide constructs can be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

[1109] The term "naked" polynucleotide, DNA or RNA, refers to sequences that are free from any delivery vehicle that acts to assist, promote, or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, the B7-like polynucleotides may also be delivered in liposome formulations (such as those taught in Felgner et al., *Ann. NY Acad. Sci.*, 772:126-139 (1995) and Abdallah et al., *Biol. Cell* , 85(1):1-7 (1995)) which can be prepared by methods well known to those skilled in the art.

[1110] The B7-like polynucleotide vector constructs used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Any strong promoter known to those skilled in the art can be used for driving the expression of DNA. Unlike other gene therapies techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

[1111] The polynucleotide constructs can be delivered to the interstitial space of tissues within the an animal, including of muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. *In vivo* muscle cells are particularly competent in their ability to take up and express polynucleotides.

[1112] For the naked B7-like polynucleotide injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 g/kg body weight to about 50 mg/kg

body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration. The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or bronchial tissues, throat or mucous membranes of the nose. In addition, naked B7-like polynucleotide constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

[1113] The dose response effects of injected B7-like polynucleotide in muscle *in vivo* is determined as follows. Suitable B7-like template DNA for production of mRNA coding for B7-like polypeptide is prepared in accordance with a standard recombinant DNA methodology. The template DNA, which may be either circular or linear, is either used as naked DNA or complexed with liposomes. The quadriceps muscles of mice are then injected with various amounts of the template DNA.

[1114] Five to six week old female and male Balb/C mice are anesthetized by intraperitoneal injection with 0.3 ml of 2.5% Avertin. A 1.5 cm incision is made on the anterior thigh, and the quadriceps muscle is directly visualized. The B7-like template DNA is injected in 0.1 ml of carrier in a 1 cc syringe through a 27 gauge needle over one minute, approximately 0.5 cm from the distal insertion site of the muscle into the knee and about 0.2 cm deep. A suture is placed over the injection site for future localization, and the skin is closed with stainless steel clips.

[1115] After an appropriate incubation time (e.g., 7 days) muscle extracts are prepared by excising the entire quadriceps. Every fifth 15 um cross-section of the individual quadriceps muscles is histochemically stained for B7-like protein expression. A time course for B7-like protein expression may be done in a similar fashion except that quadriceps from different mice are harvested at different times. Persistence of B7-like DNA in muscle following injection may be determined by Southern blot analysis after preparing total cellular DNA and HIRT supernatants from injected and control mice. The results of the above experimentation in mice can be use to extrapolate proper dosages and other treatment parameters in humans

and other animals using B7-like naked DNA.

Example 16: Production of an Antibody

a) Hybridoma Technology

[1116] The antibodies of the present invention can be prepared by a variety of methods. (See, Current Protocols, Chapter 2.) As one example of such methods, cells expressing B7-like polypeptide(s) are administered to an animal to induce the production of sera containing polyclonal antibodies. In a preferred method, a preparation of B7-like polypeptide(s) is prepared and purified to render it substantially free of natural contaminants. Such a preparation is then introduced into an animal in order to produce polyclonal antisera of greater specific activity.

[1117] Monoclonal antibodies specific for B7-like polypeptide(s) are prepared using hybridoma technology. (Kohler et al., Nature 256:495 (1975); Kohler et al., Eur. J. Immunol. 6:511 (1976); Kohler et al., Eur. J. Immunol. 6:292 (1976); Hammerling et al., in: Monoclonal Antibodies and T-Cell Hybridomas, Elsevier, N.Y., pp. 563-681 (1981)). In general, an animal (preferably a mouse) is immunized with B7-like polypeptide(s) or, more preferably, with a secreted B7-like polypeptide-expressing cell. Such polypeptide-expressing cells are cultured in any suitable tissue culture medium, preferably in Earle's modified Eagle's medium supplemented with 10% fetal bovine serum (inactivated at about 56°C), and supplemented with about 10 g/l of nonessential amino acids, about 1,000 U/ml of penicillin, and about 100 μg/ml of streptomycin.

[1118] The splenocytes of such mice are extracted and fused with a suitable myeloma cell line. Any suitable myeloma cell line may be employed in accordance with the present invention; however, it is preferable to employ the parent myeloma cell line (SP2O), available from the ATCC. After fusion, the resulting hybridoma cells are selectively maintained in HAT medium, and then cloned by limiting dilution as described by Wands et al. (Gastroenterology 80:225-232 (1981)). The hybridoma cells obtained through such a selection are then assayed to identify clones which secrete antibodies capable of binding the B7-like polypeptide(s).

[1119] Alternatively, additional antibodies capable of binding to B7-like polypeptide(s) can be produced in a two-step procedure using anti-idiotypic antibodies. Such a method

makes use of the fact that antibodies are themselves antigens, and therefore, it is possible to obtain an antibody which binds to a second antibody. In accordance with this method, protein specific antibodies are used to immunize an animal, preferably a mouse. The splenocytes of such an animal are then used to produce hybridoma cells, and the hybridoma cells are screened to identify clones which produce an antibody whose ability to bind to the B7-like protein-specific antibody can be blocked by B7-like polypeptide(s). Such antibodies comprise anti-idiotypic antibodies to the B7-like protein-specific antibody and are used to immunize an animal to induce formation of further B7-like protein-specific antibodies.

[1120] For in vivo use of antibodies in humans, an antibody is "humanized". Such antibodies can be produced using genetic constructs derived from hybridoma cells producing the monoclonal antibodies described above. Methods for producing chimeric and humanized antibodies are known in the art and are discussed herein. (See, for review, Morrison, Science 229:1202 (1985); Oi et al., BioTechniques 4:214 (1986); Cabilly et al., U.S. Patent No. 4,816,567; Taniguchi et al., EP 171496; Morrison et al., EP 173494; Neuberger et al., WO 8601533; Robinson et al., WO 8702671; Boulianne et al., Nature 312:643 (1984); Neuberger et al., Nature 314:268 (1985)).

b) Isolation Of Antibody Fragments Directed Against B7-like Polypeptide(s) From A Library Of scFvs

[1121] Naturally occurring V-genes isolated from human PBLs are constructed into a library of antibody fragments which contain reactivities against B7-like polypeptide(s) to which the donor may or may not have been exposed (see e.g., U.S. Patent 5,885,793 incorporated herein by reference in its entirety).

Rescue of the Library.

[1122] A library of scFvs is constructed from the RNA of human PBLs as described in PCT publication WO 92/01047. To rescue phage displaying antibody fragments, approximately 109 E. coli harboring the phagemid are used to inoculate 50 ml of 2xTY containing 1% glucose and 100 µg/ml of ampicillin (2xTY-AMP-GLU) and grown to an O.D. of 0.8 with shaking. Five ml of this culture is used to innoculate 50 ml of 2xTY-AMP-GLU, 2 x 108 TU of delta gene 3 helper (M13 delta gene III, see PCT publication WO 92/01047) are added and the culture incubated at 37°C for 45 minutes without shaking and

then at 37°C for 45 minutes with shaking. The culture is centrifuged at 4000 r.p.m. for 10 min. and the pellet resuspended in 2 liters of 2xTY containing 100 μg/ml ampicillin and 50 μg/ml kanamycin and grown overnight. Phage are prepared as described in PCT publication WO 92/01047.

[1123] M13 delta gene III is prepared as follows: M13 delta gene III helper phage does not encode gene III protein, hence the phage(mid) displaying antibody fragments have a greater avidity of binding to antigen. Infectious M13 delta gene III particles are made by growing the helper phage in cells harboring a pUC19 derivative supplying the wild type gene III protein during phage morphogenesis. The culture is incubated for 1 hour at 37° C without shaking and then for a further hour at 37°C with shaking. Cells are spun down (IEC-Centra 8,400 r.p.m. for 10 min), resuspended in 300 ml 2xTY broth containing 100 μg ampicillin/ml and 25 μg kanamycin/ml (2xTY-AMP-KAN) and grown overnight, shaking at 37°C. Phage particles are purified and concentrated from the culture medium by two PEG-precipitations (Sambrook et al., 1990), resuspended in 2 ml PBS and passed through a 0.45 μm filter (Minisart NML; Sartorius) to give a final concentration of approximately 1013 transducing units/ml (ampicillin-resistant clones).

Panning of the Library.

[1124] Immunotubes (Nunc) are coated overnight in PBS with 4 ml of either 100 μg/ml or 10 μg/ml of a polypeptide of the present invention. Tubes are blocked with 2% Marvel-PBS for 2 hours at 37°C and then washed 3 times in PBS. Approximately 1013 TU of phage is applied to the tube and incubated for 30 minutes at room temperature tumbling on an over and under turntable and then left to stand for another 1.5 hours. Tubes are washed 10 times with PBS 0.1% Tween-20 and 10 times with PBS. Phage are eluted by adding 1 ml of 100 mM triethylamine and rotating 15 minutes on an under and over turntable after which the solution is immediately neutralized with 0.5 ml of 1.0M Tris-HCl, pH 7.4. Phage are then used to infect 10 ml of mid-log E. coli TG1 by incubating eluted phage with bacteria for 30 minutes at 37°C. The E. coli are then plated on TYE plates containing 1% glucose and 100 μg/ml ampicillin. The resulting bacterial library is then rescued with delta gene 3 helper phage as described above to prepare phage for a subsequent round of selection. This process is then repeated for a total of 4 rounds of affinity purification with tube-washing increased to 20 times with PBS, 0.1% Tween-20 and 20 times with PBS for rounds 3 and 4.

Characterization of Binders.

[1125] Eluted phage from the 3rd and 4th rounds of selection are used to infect E. coli HB 2151 and soluble scFv is produced (Marks, et al., 1991) from single colonies for assay. ELISAs are performed with microtitre plates coated with either 10 pg/ml of the polypeptide of the present invention in 50 mM bicarbonate pH 9.6. Clones positive in ELISA are further characterized by PCR fingerprinting (see, e.g., PCT publication WO 92/01047) and then by sequencing. These ELISA positive clones may also be further characterized by techniques known in the art, such as, for example, epitope mapping, binding affinity, receptor signal transduction, ability to block or competitively inhibit antibody/antigen binding, and competitive agonistic or antagonistic activity.

Example 17: B7-like Knock-Out Animals

[1126] Endogenous B7-like gene expression can also be reduced by inactivating or "knocking out" the B7-like gene and/or its promoter using targeted homologous recombination. (E.g., see Smithies et al., Nature 317:230-234 (1985); Thomas & Capecchi, Cell 51:503-512 (1987); Thompson et al., Cell 5:313-321 (1989); each of which is incorporated by reference herein in its entirety). For example, a mutant, non-functional polynucleotide of the invention (or a completely unrelated DNA sequence) flanked by DNA homologous to the endogenous polynucleotide sequence (either the coding regions or regulatory regions of the gene) can be used, with or without a selectable marker and/or a negative selectable marker, to transfect cells that express polypeptides of the invention in vivo. In another embodiment, techniques known in the art are used to generate knockouts in cells that contain, but do not express the gene of interest. Insertion of the DNA construct, via targeted homologous recombination, results in inactivation of the targeted gene. Such approaches are particularly suited in research and agricultural fields where modifications to embryonic stem cells can be used to generate animal offspring with an inactive targeted gene (e.g., see Thomas & Capecchi 1987 and Thompson 1989, supra). However this approach can be routinely adapted for use in humans provided the recombinant DNA constructs are directly administered or targeted to the required site in vivo using appropriate viral vectors that will be apparent to those of skill in the art.

[1127] In further embodiments of the invention, cells that are genetically engineered to express the polypeptides of the invention, or alternatively, that are genetically engineered not to express the polypeptides of the invention (e.g., knockouts) are administered to a patient in vivo. Such cells may be obtained from the patient (i.e., animal, including human) or an MHC compatible donor and can include, but are not limited to fibroblasts, bone marrow cells, blood cells (e.g., lymphocytes), adipocytes, muscle cells, endothelial cells etc. The cells are genetically engineered in vitro using recombinant DNA techniques to introduce the coding sequence of polypeptides of the invention into the cells, or alternatively, to disrupt the coding sequence and/or endogenous regulatory sequence associated with the polypeptides of the invention, e.g., by transduction (using viral vectors, and preferably vectors that integrate the transgene into the cell genome) or transfection procedures, including, but not limited to, the use of plasmids, cosmids, YACs, naked DNA, electroporation, liposomes, etc. The coding sequence of the polypeptides of the invention can be placed under the control of a strong constitutive or inducible promoter or promoter/enhancer to achieve expression, and preferably secretion, of the B7-like polypeptides. The engineered cells which express and preferably secrete the polypeptides of the invention can be introduced into the patient systemically, e.g., in the circulation, or intraperitoneally.

[1128] Alternatively, the cells can be incorporated into a matrix and implanted in the body, e.g., genetically engineered fibroblasts can be implanted as part of a skin graft; genetically engineered endothelial cells can be implanted as part of a lymphatic or vascular graft. (See, for example, Anderson et al. U.S. Patent No. 5,399,349; and Mulligan & Wilson, U.S. Patent No. 5,460,959 each of which is incorporated by reference herein in its entirety).

[1129] When the cells to be administered are non-autologous or non-MHC compatible cells, they can be administered using well known techniques which prevent the development of a host immune response against the introduced cells. For example, the cells may be introduced in an encapsulated form which, while allowing for an exchange of components with the immediate extracellular environment, does not allow the introduced cells to be recognized by the host immune system.

[1130] Knock-out animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of B7-like polypeptides, studying conditions and/or disorders associated with aberrant B7-like expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

Example 18: B7-like Counter-Receptor Expression

[1131] To detect the expression of counter-receptor(s) of B7-like molecules, expression of activated markers on T cells are analyzed with FITC-conjugated mAb specific to CD25, CD40L, 4-1BB and OX40. Single or double stained cells are analyzed using the Becton-Dickinson FACScan (Mountain View, CA).

Example 19: T Cell Proliferation and Cytokine Assays

[1132] Methods for measuring T cell growth and cytokine production were described previously (Dong, H., *et al., Nat Med., 5*:1365-9 (1999)). Briefly, flat-bottomed 96-well plates are first coated at 4°C overnight with 50 μl/well of anti-CD3 mAb at 40 or 200 ng/ml and subsequently coated with B7-H3Ig or control Ig at 37°C for 4 hrs. T cells at indicated concentrations are cultured for 72 hrs and ^{3}H-TdR at 1 μCi/well is added for the last 18 hrs., and the ^{3}H-TdR incorporation is counted on a Microbeta Trilix liquid scintillation counter (Wallac, Turku, Finland). Supernatants are collected 48 hrs after T cell culturing, and are assayed for IL-2, IL-10, and IFN-γ using appropriate sandwich ELISA as described by Dong et al. utilizing mAb purchased from Pharmingen.

Example 20: T Cell Proliferation, Costimulation, and Prestimulation Proliferation Assays

Proliferation assay for Resting PBLs.

[1133] A CD3-induced proliferation assay is performed on PBMCs and is measured by the uptake of ^{3}H-thymidine. The assay is performed as follows. Ninety-six well plates are coated with 100 microliters per well of mAb to CD3 (HIT3a, Pharmingen) or isotype-matched control mAb (B33.1) overnight at 4°C (1 microgram/ml in .05M bicarbonate buffer, pH 9.5), then washed three times with PBS. PBMC are isolated by Ficoll/Hypaque (F/H) gradient centrifugation from human peripheral blood and added to quadruplicate wells (5 x 10^4/well) of mAb coated plates in RPMI containing 10% FCS and Penicillin and Streptomycin (P/S) in the presence of varying concentrations of B7-like protein (total volume 200 microliters). Relevant protein buffer and medium alone are controls. After 48 hr. culture at 37 C, plates are spun for 2 min. at 1000 rpm and 100 microliters of supernatant is removed and stored –20°C for measurement of IL-2 (or other cytokines) if effect on proliferation is observed. Wells are supplemented with 100 microliters of medium containing 0.5

microcuries of ^{3}H-thymidine and cultured at 37°C for 18-24 hr. Wells are harvested and incorporation of ^{3}H-thymidine used as a measure of proliferation. Anti-CD3 alone is the positive control for proliferation. IL-2 (100 U/ml) is also used as a control which enhances proliferation. Control antibody which does not induce proliferation of T cells is used as the negative controls for the effects of B7-like proteins.

[1134] Alternatively, a proliferation assay on resting PBL (peripheral blood lymphocytes) is measured by the up-take of ^{3}H-thymidine. The assay is performed as follows. PBMC are isolated by F/H gradient centrifugation from human peripheral blood, and are cultured overnight in 10% FCS/RPMI. This overnight incubation period allows the adherent cells to attach to the plastic, which results in a lower background in the assay as there are fewer cells that can act as antigen presenting cells or that might be producing growth factors. The following day the non-adherent cells are collected, washed and used in the proliferation assay. The assay is performed in a 96 well plate using 2 x10^4 cells/well in a final volume of 200 microliters. A supernatant expressing the B7-like polypeptide of interest is tested at a 30% final dilution, therefore 60 microliters are added to 140 microliters of medium containing the cells. Control supernatants are used at the same final dilution and express the following proteins: vector only (negative control), IL-2, IFNgamma, TNF-alpha, IL-10 and TR2. In addition to the control supernatants recombinant human IL-2 at a final concentration of 100 ng/ml is also used. After 24 hours of culture, each well is pulsed with 1 microcurie of ^{3}H-thymidine. Cells are then harvested 20 hours following pulsing and incorporation of ^{3}H-thymidine is used as a measure of proliferation. Results are expressed as an average of triplicate samples plus or minus standard error.

Costimulation assay.

[1135] A costimulation assay on resting PBL (peripheral blood lymphocytes) is performed in the presence of immobilized antibodies to CD3 and CD28. The use of antibodies specific for the invariant regions of CD3 mimic the induction of T cell activation that would occur through stimulation of the T cell receptor by an antigen. Cross-linking of the TCR (first signal) in the absence of a costimulatory signal (second signal) causes very low induction of proliferation and will eventually result in a state of "anergy", which is characterized by the absence of growth and inability to produce cytokines. The addition of a costimulatory signal such as an antibody to CD28, which mimics the action of the costimulatory molecule B7-1

expressed on activated APCs, results in enhancement of T cell responses including cell survival and production of IL-2. Therefore this type of assay allows to detect both positive and negative effects caused by addition of supernatants expressing the proteins of interest on T cell proliferation.

[1136] The assay is performed as follows. Ninety-six well plates are coated with 100 ng/ml anti-CD3 and 5 micrograms per milliliter anti-CD28 in a final volume of 100 microliters and incubated overnight at 4 C. Plates are washed twice with PBS before use. PBMC are isolated by F/H gradient centrifugation from human peripheral blood, and are cultured overnight in 10% FCS/RPMI. This overnight incubation period allows the adherent cells to attach to the plastic, which results in a lower background in the assay as there are fewer cells that can act as antigen presenting cells or that might be producing growth factors. The following day the non-adherent cells are collected, washed and used in the proliferation assay. The assay is performed in a 96 well plate using 2 x10^4 cells/well in a final volume of 200 microliters. A supernatant expressing the B7-like polypeptide of interest is tested at a 30% final dilution, therefore 60 microliters are added to 140 microliters of medium containing the cells. Control supernatants are used at the same final dilution and express the following proteins: vector only (negative control), IL-2, IFN-gamma, TNF-alpha, IL-10 and TR2. In addition to the control supernatants recombinant human IL-2 at a final concentration of 10 ng/ml is also used. After 24 hours of culture, each well is pulsed with 1 microcurie of ^{3}H-thymidine. Cells are then harvested 20 hours following pulsing and incorporation of ^{3}H-thymidine is used as a measure of proliferation. Results are expressed as an average of triplicate samples plus or minus standard error.

Proliferation assay for preactivated-resting T cells.

[1137] A proliferation assay on preactivated-resting T cells is performed on cells that are previously activated with the lectin phytohemagglutinin (PHA). Lectins are polymeric plant proteins that can bind to residues on T cell surface glycoproteins including the TCR and act as polyclonal activators. PBLs treated with PHA and then cultured in the presence of low doses of IL-2 resemble effector T cells. These cells are generally more sensitive to further activation induced by growth factors such as IL-2. This is due to the expression of high affinity IL-2 receptors that allows this population to respond to amounts of IL-2 that are 100 fold lower than what would have an effect on a naïve T cell. Therefore the use of this type of

cells might enable to detect the effect of very low doses of an unknown growth factor, that would not be sufficient to induce proliferation on resting (naïve) T cells.

[1138] The assay is performed as follows. PBMC are isolated by F/H gradient centrifugation from human peripheral blood, and are cultured in the presence of 2 micrograms per milliliter PHA for three days. The cells are then washed and cultured in the presence of 5 ng/ml of human recombinant IL-2 for 3 days. The cells are washed and rested in starvation medium (1% FCS/RPMI) for 16 hours prior to the beginning of the proliferation assay. An aliquot of the cells is analyzed by FACS to determine the percentage of T cells (CD3 positive cells), usually it ranges between 93-97% depending on the donor. The assay is performed in a 96 well plate using 2 $x10^4$ cells/well in a final volume of 200 microliters. A supernatant expressing the B7-like polypeptide of interest is tested at a 30% final dilution, therefore 60 microliters are added to 140 microliters of medium containing the cells. Control supernatants are used at the same final dilution and express the following proteins: vector only (negative control), IL-2, IFN-gamma, TNF-alpha, IL-10 and TR2. In addition to the control supernatants recombinant human IL-2 at a final concentration of 10 ng/ml is also used. After 24 hours of culture, each well is pulsed with 1 microcurie of ^{3}H-thymidine. Cells are then harvested 20 hours following pulsing and incorporation of ^{3}H-thymidine is used as a measure of proliferation. Results are expressed as an average of triplicate samples plus or minus standard error.

[1139] Although the studies described in this example test the activity in B7-like protein, one skilled in the art could easily modify the exemplified studies to test the activity of B7-like polynucleotides (e.g., gene therapy), agonists, and/or antagonists of B7-like.

[1140] It will be clear that the invention may be practiced otherwise than as particularly described in the foregoing description and examples. Numerous modifications and variations of the present invention are possible in light of the above teachings and, therefore, are within the scope of the appended claims.

[1141] The entire disclosure of each document cited (including patents, patent applications, journal articles, abstracts, laboratory manuals, books, or other disclosures) in the Background of the Invention, Detailed Description, and Examples is hereby incorporated herein by reference. Further, the hard copy of the sequence listing submitted herewith and the

corresponding computer readable form are both incorporated herein by reference in their entireties.

[1142] Certain B7-like polynucleotides and polypeptides of the present invention, including antibodies, were disclosed in U.S. provisional application numbers 60/215,135 and 60/225,266, the specifications and sequence listings of which are herein incorporated by reference in their entirety.

CLAIMS

1. An isolated nucleic acid molecule comprising a polynucleotide selected from the group consisting of:

(a) the polynucleotide shown as SEQ ID NO:X or the polynucleotide encoded by a cDNA included in ATCC Deposit No:Z;

(b) a polynucleotide encoding a biologically active polypeptide fragment of SEQ ID NO:Y or a biologically active polypeptide fragment encoded by the cDNA sequence included in ATCC Deposit No:Z;

(c) a polynucleotide encoding a polypeptide epitope of SEQ ID NO:Y or a polypeptide epitope encoded by the cDNA sequence included in ATCC Deposit No:Z;

(d) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(c), wherein said polynucleotide does not hybridize under stringent conditions to a nucleic acid molecule having a nucleotide sequence of only A residues or of only T residues.

2. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide comprises a nucleotide sequence encoding a soluble polypeptide.

3. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide comprises a nucleotide sequence encoding the sequence identified as SEQ ID NO:Y or the polypeptide encoded by the cDNA sequence included in ATCC Deposit No:Z.

4. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide comprises the entire nucleotide sequence of SEQ ID NO:X or a cDNA included in ATCC Deposit No:Z.

5. The isolated nucleic acid molecule of claim 2, wherein the polynucleotide is DNA.

6. The isolated nucleic acid molecule of claim 3, wherein the polynucleotide is RNA.

7. A vector comprising the isolated nucleic acid molecule of claim 1.

8. A host cell comprising the vector of claim 7.

9. A recombinant host cell comprising the nucleic acid molecule of claim 1 operably limited to a heterologous regulating element which controls gene expression.

10. A method of producing a polypeptide comprising expressing the encoded polypeptide from the host cell of claim 9 and recovering said polypeptide.

11. An isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence selected from the group consisting of:

(a) the polypeptide shown as SEQ ID NO:Y or the polypeptide encoded by the cDNA;

(b) a polypeptide fragment of SEQ ID NO:Y or the polypeptide encoded by the cDNA;

(c) a polypeptide epitope of SEQ ID NO:Y or the polypeptide encoded by the cDNA; and

(d) a variant of SEQ ID NO:Y.

12. The isolated polypeptide of claim 11, comprising a polypeptide having SEQ ID NO:Y.

13. An isolated antibody that binds specifically to the isolated polypeptide of claim 11.

14. A recombinant host cell that expresses the isolated polypeptide of claim 11.

15. A method of making an isolated polypeptide comprising:

(a) culturing the recombinant host cell of claim 14 under conditions such that said polypeptide is expressed; and

(b) recovering said polypeptide.

16. The polypeptide produced by claim 15.

17. A method for preventing, treating, or ameliorating a medical condition, comprising administering to a mammalian subject a therapeutically effective amount of the polynucleotide of claim 1.

18. A method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising:

(a) determining the presence or absence of a mutation in the polynucleotide of claim 1; and

(b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or absence of said mutation.

19. A method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising:

(a) determining the presence or amount of expression of the polypeptide of claim 11 in a biological sample; and

(b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or amount of expression of the polypeptide.

20. A method for identifying a binding partner to the polypeptide of claim 11 comprising:

(a) contacting the polypeptide of claim 11 with a binding partner; and

(b) determining whether the binding partner effects an activity of the polypeptide.

21. A method of screening for molecules which modify activities of the polypeptide of claim 11 comprising:

(a) contacting said polypeptide with a compound suspected of having agonist or antagonist activity; and

(b) assaying for activity of said polypeptide.

22. A method for preventing, treating, or ameliorating a medical condition, comprising administering to a mammalian subject a therapeutically effective amount the polypeptide of claim 11.

Figure 1A

```
  1  CACCAGCAGTAGTAGCAGAAGCGAAGAGCGCAAACGCAACCGCTCTCCCCGCGCGTTGGC   60

 61  CGATTCATTAATGCAGCTGGCACGACAGGTTTCCCGACTGGAAAGCGGGCAGTGAGCGCA  120

121  ACGCAATTAATGTGAGTTAGCTCACTCATTAGGCACCCCAGGCTTTACACTTTATGCTTC  180

181  CGGCTCGTATGTTGTGTGGAATTGTGAGCGGATAACAATTTCACACAGGAAACAGCTATG  240

241  ACCATGATTACGCCAAGCTCGAAATTAACCCTCACTAAAGGGAACAAAAGCTGGAGCTCC  300

301  ACCGCGGTGGCGGCCGCTCTAGAACTAGTGGATCCCCCGGGCTGCAGGAATTCGGCACGA  360

361  GAGGCAGCGGCAGCTCCACTCAGCCAGTACCCAGATACGCTGGGAACCTTCCCCAGCCAT  420
  1                                                           M    1

421  GGCTTCCCTGGGGCAGATCCTCTTCTGGAGCATAATTAGCATCATCATTATTCTGGCTGG  480
  2   A  S  L  G  Q  I  L  F  W  S  I  I  S  I  I  I  I  L  A  G   21

481  AGCAATTGCACTCATCATTGGCTTTGGTATTTCAGGGAGACACTCCATCACAGTCACTAC  540
 22   A  I  A  L  I  I  G  F  G  I  S  G  R  H  S  I  T  V  T  T   41

541  TGTCGCCTCAGCTGGGAACATTGGGGAGGATGGAATCCTGAGCTGCACTTTTGAACCTGA  600
 42   V  A  S  A  G  N  I  G  E  D  G  I  L  S  C  T  F  E  P  D   61

601  CATCAAACTTTCTGATATCGTGATACAATGGCTGAAGGAAGGTGTTTTAGGCTTGGTCCA  660
 62   I  K  L  S  D  I  V  I  Q  W  L  K  E  G  V  L  G  L  V  H   81

661  TGAGTTCAAAGAAGGCAAAGATGAGCTGTCGGAGCAGGATGAAATGTTCAGAGGCCGGAC  720
 82   E  F  K  E  G  K  D  E  L  S  E  Q  D  E  M  F  R  G  R  T  101

721  AGCAGTGTTTGCTGATCAAGTGATAGTTGGCAATGCCTCTTTGCGGCTGAAAAACGTGCA  780
102   A  V  F  A  D  Q  V  I  V  G  N  A  S  L  R  L  K  N  V  Q  121

781  ACTCACAGATGCTGGCACCTACAAATGTTATATCATCACTTCTAAAGGCAAGGGGAATGC  840
122   L  T  D  A  G  T  Y  K  C  Y  I  I  T  S  K  G  K  G  N  A  141

841  TAACCTTGAGTATAAAACTGGAGCCTTCAGCATGCCGGAAGTGAATGTGGACTATAATGC  900
142   N  L  E  Y  K  T  G  A  F  S  M  P  E  V  N  V  D  Y  N  A  161

901  CAGCTCAGAGACCTTGCGGTGTGAGGCTCCCCGATGGTTCCCCCAGCCCACAGTGGTCTG  960
162   S  S  E  T  L  R  C  E  A  P  R  W  E  P  Q  P  T  V  V  W  181
```

Figure 1B

```
 961  GGCATCCCAAGTTGACCAGGGAGCCAACTTCTCGGAAGTCTCCAATACCAGCTTTGAGCT  1020
 182   A  S  Q  V  D  Q  G  A  N  F  S  E  V  S  N  T  S  F  E  L   201

1021  GAACTCTGAGAATGTGACCATGAAGGTTGTGTCTGTGCTCTACAATGTTACGATCAACAA  1080
 202   N  S  E  N  V  T  M  K  V  V  S  V  L  Y  N  V  T  I  N  N   221

1081  CACATACTCCTGTATGATTGAAAATGACATTGCCAAAGCAACAGGGGATATCAAAGTGAC  1140
 222   T  Y  S  C  M  I  E  N  D  I  A  K  A  T  G  D  I  K  V  T   241

1141  AGAATCGGAGATCAAAAGGCGGAGTCACCTACAGCTGCTAAACTCAAAGGCTTCTCTGTG  1200
 242   E  S  E  I  K  R  R  S  H  L  Q  L  L  N  S  K  A  S  L  C   261

1201  TGTCTCTTCTTTCTTTGCCATCAGCTGGGCACTTCTGCCTCTCAGCCCTTACCTGATGCT  1260
 262   V  S  S  F  F  A  I  S  W  A  L  L  P  L  S  P  Y  L  M  L   281

1261  AAAATAATGTGCCTTGGCCACAAAAAAGCATGCAAAGTCATTGTTACAACAGGGATCTAC  1320
 282   K  *                                                         283

1321  AGAACTATTTCACCACCAGATATGACCTAGTTTTATATTTCTGGGAGGAAATGAATTCAT  1380

1381  ATCTAGAAGTCTGGAGTGAGCAAACAAGAGCAAGAAACAAAAAGAAGCCAAAAGCAGAAG  1440

1441  GCTCCAATATGAACAAGATAAATCTATCTTCAAAGACATATTAGAAGTTGGAAAAATAAT  1500

1501  TCATGTGAACTAGACAAGTGTGTTAAGAGTGATAAGTAAAATGCACGTGGAGACAAGTGC  1560

1561  ATCCCCAGATCTCAGGGACCTCCCCCTGCCTGTCACCTGGGGAGTGAGAGGACAGGATAG  1620

1621  TGCATGTTCTTTGTCTCTGAATTTTTAGTTATATGTGCTGTAATGTTGCTCTGAGGAAGC  1680

1681  CCCTGGAAAGTCTATCCCAACATATCCACATCTTATATTCCACAAATTAAGCTGTAGTAT  1740

1741  GTACCCTAAGACGCTGCTAATCGACTGCCACTTCGCAACTCAGGGGCGGCTGCATTTTAG  1800

1801  TAATGGGTCAAATGATTCACTTTTTATGATGCTTCCAAAGGTGCCTTGGCTTCTCTTCCC  1860

1861  AACTGACAAATGCCAAAGTTGAGAAAAATGATCATAATTTTAGCATAAACAGAGCAGTCG  1920

1921  GCGACACCGATTTTATAAATAAACTGAGCACCTTCTTTTTAAACAAACAAATGCGGGTTT  1980
```

Figure 1C

1981 ATTTCTCAGATGATGTTCATCCGTGAATGGTCCAGGGAAGGACCTTTCACCTTGACTATA 2040

2041 TGGCATTATGTCATCACAAGCTCTGAGGCTTCTCCTTTCCATCCTGCGTGGACAGCTAAG 2100

2101 ACCTCAGTTTTCAATAGCATCTAGAGCAGTGGGACTCAGCTGGGGTGATTTCGCCCCCCA 2160

2161 TCTCCGGGGGAATGTCTGAAGACAATTTTGGTTACCTCAATGAGGGAGTGGAGGAGGATA 2220

2221 CAGTGCTACTACCAACTAGTGGATAAAGGCCAGGGATGCTGCTCAACCTCCTACCATGTA 2280

2281 CAGGACGTCTCCCCATTACAACTACCCAATCCGAAGTGTCAACTGTGTCAGGACTAAGAA 2340

2341 ACCCTGGTTTTGAGTAGAAAAGGGCCTGGAAAGAGGGGAGCCAACAAATCTGTCTGCTTC 2400

2401 CTCACATTAGTCATTGGCAAATAAGCATTCTGTCTCTTTGGCTGCTGCCTCAGCACAGAG 2460

2461 AGCCAGAACTCTATCGGGCACCAGGATAACATCTCTCAGTGAACAGAGTTGACAAGGCCT 2520

2521 ATGGGAAATGCCTGATGGGATTATCTTCAGCTTGTTGAGCTTCTAAGTTTCTTTCCCTTC 2580

2581 ATTCTACCCTGCAAGCCAAGTTCTGTAAGAGAAATGCCTGAGTTCTAGCTCAGGTTTTCT 2640

2641 TACTCTGAATTTAGATCTCCAGACCCTTCCTGGCCACAATTCAAATTAAGGCAACAAACA 2700

2701 TATACCTTCCATGAAGCACACACAGACTTTTGAAAGCAAGGACAATGACTGCTTGAATTG 2760

2761 AGGCCTTGAGGAATGAAGCTTTGAAGGAAAAGAATACTTTGTTTCCAGCCCCCTTCCCAC 2820

2821 ACTCTTCATGTGTTAACCACTGCCTTCCTGGACCTTGGAGCCACGGTGACTGTATTACAT 2880

2881 GTTGTTATAGAAAACTGATTTTAGAGTTCTGATCGTTCAAGAGAATGATTAAATATACAT 2940

2941 TTCCTAAAAAAAAAAAAAAAAAAACTCGAGGGGGGCCCGGTACCCAATTCGCCCTATAGT 3000

3001 GAGTCGTATTACAATTCACTGGCCGTCGTTTTACAACGTCGTGACTGGGAAAACCCTGGC 3060

3061 GTTACCCAACTTAATCGCCTTGCAGCACATCCCCCTTTCGCCAGCTGGCGTAATAGCGAA 3120

Figure 1D

```
3121  GAGGCCCGCACCGATCGCCCTTCCCAACAKTTGCGCAGCCTGAATGGCGAATGGCAAATT   3180

3181  GTAAGCGTTAATATTTTGTTAAAATTCGCGTTAAATTTTTGTTAAATCAGCTCATTTTTT   3240

3241  AACCAATAGGCCGAAATCGGCAAAATCCCTTATAAATCAAAAGAATAGACCGAGATAGGG   3300

3301  TTGAGTGTTGTTCCAGTTTGGAACAAGAGTCCACTATTAAAGTGTTCACCGCGGTGA   3357
```

Figure 2

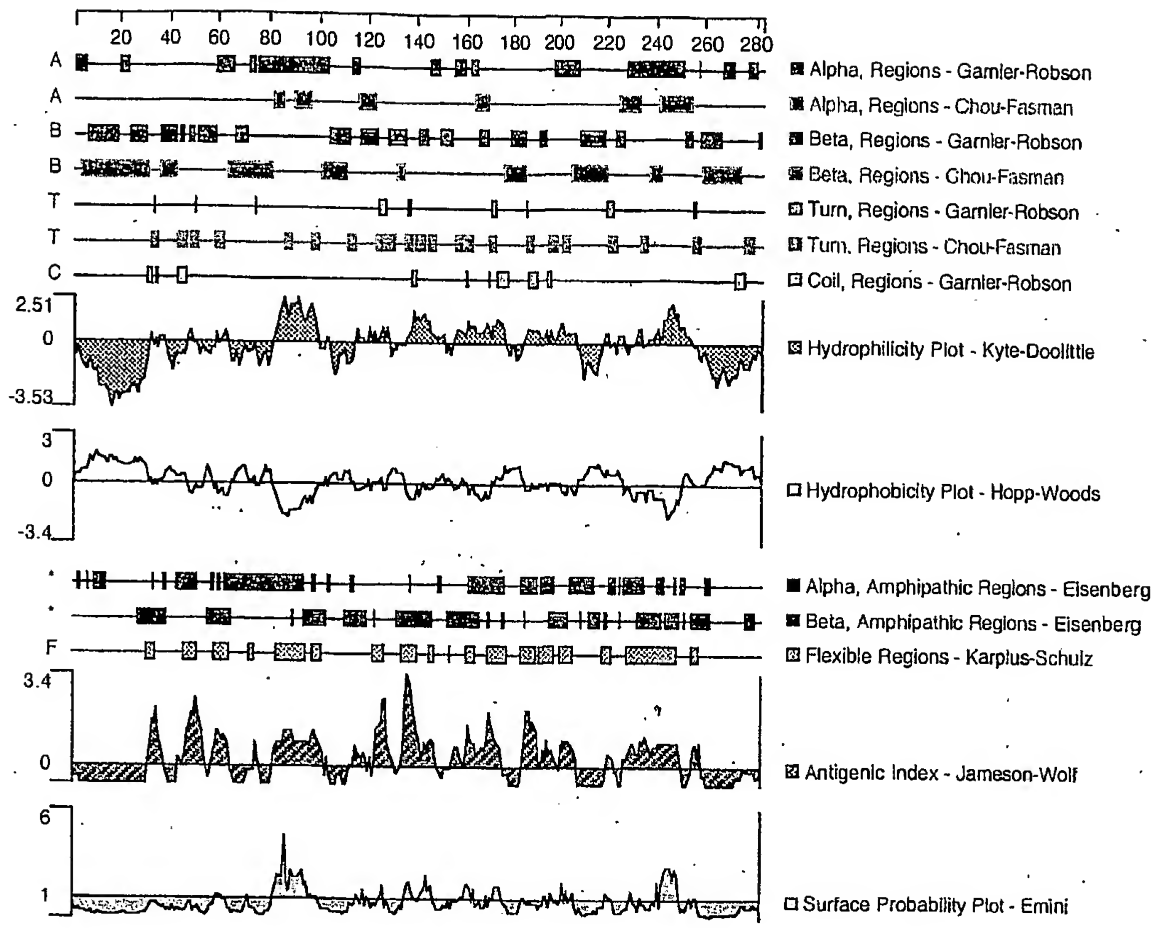

20 40 60 80 100 120 140 160 180 200 220 240 260 280
A
A
B
B
T
T
C
2.51
0
-3.53
3
0
-3.4
F
3.4
0
6
1
Alpha, Regions - Garnier-Robson
Alpha, Regions - Chou-Fasman
Beta, Regions - Garnier-Robson
Beta, Regions - Chou-Fasman
Turn, Regions - Garnier-Robson
Turn, Regions - Chou-Fasman
Coil, Regions - Garnier-Robson
Hydrophilicity Plot - Kyte-Doolittle
Hydrophobicity Plot - Hopp-Woods
Alpha, Amphipathic Regions - Eisenberg
Beta, Amphipathic Regions - Eisenberg
Flexible Regions - Karplus-Schulz
Antigenic Index - Jameson-Wolf
Surface Probability Plot - Emini

Figure 3A

```
  1 CCACGCGTCCGGAATGAACAACTTTTCTTCTCTTGAATATATCTTAACGCCAAATTTTGA  60

 61 GTGCTTTTTTGTTACCCATCCTCATATGTCCCAGCTGGAAAGAATCCTGGGTTGGAGCTA 120

121 CTGCATGTTGATTGTTTTGTTTTTCCTTTTGGCTGTTCATTTTGGTGGCTACTATAAGGA 180

181 AATCTAACACAAACAGCAACTGTTTTTGTTGTTTACTTTTGCATCTTTACTTGTGGAGC  240

241 TGTGGCAAGTCCTCATATCAAATACAGAACATGATCTTCCTCCTGCTAATGTTGAGCCTG 300
  1                               M  I  F  L  L  L  M  L  S  L   10

301 GAATTGCAGCTTCACCAGATAGCAGCTTTATTCACAGTGACAGTCCCTAAGGAACTGTAC 360
 11 E  L  Q  L  H  Q  I  A  A  L  F  T  V  T  V  P  K  E  L  Y   30

361 ATAATAGAGCATGGCAGCAATGTGACCCTGGAATGCAACTTTGACACTGGAAGTCATGTG 420
 31 I  I  E  H  G  S  N  V  T  L  E  C  N  F  D  T  G  S  H  V   50

421 AACCTTGGAGCAATAACAGCCAGTTTGCAAAAGGTGGAAAATGATACATCCCCACACCGT 480
 51 N  L  G  A  I  T  A  S  L  Q  K  V  E  N  D  T  S  P  H  R   70

481 GAAAGAGCCACTTTGCTGGAGGAGCAGCTGCCCCTAGGGAAGGCCTCGTTCCACATACCT 540
 71 E  R  A  T  L  L  E  E  Q  L  P  L  G  K  A  S  F  H  I  P   90

541 CAAGTCCAAGTGAGGGACGAAGGACAGTACCAATGCATAATCATCTATGGGGTCGCCTGG 600
 91 Q  V  Q  V  R  D  E  G  Q  Y  Q  C  I  I  I  Y  G  V  A  W  110

601 GACTACAAGTACCTGACTCTGAAAGTCAAAGCTTCCTACAGGAAAATAAACACTCACATC 660
111 D  Y  K  Y  L  T  L  K  V  K  A  S  Y  R  K  I  N  T  H  I  130

661 CTAAAGGTTCCAGAAACAGATGAGGTAGAGCTCACCTGCCAGGCTACAGGTTATCCTCTG 720
131 L  K  V  P  E  T  D  E  V  E  L  T  C  Q  A  T  G  Y  P  L  150

721 GCAGAAGTATCCTGGCCAAACGTCAGCGTTCCTGCCAACACCAGCCACTCCAGGACCCCT 780
151 A  E  V  S  W  P  N  V  S  V  P  A  N  T  S  H  S  R  T  P  170

781 GAAGGCCTCTACCAGGTCACCAGTGTTCTGCGCCTAAAGCCACCCCCTGGCAGAAACTTC 840
171 E  G  L  Y  Q  V  T  S  V  L  R  L  K  P  P  P  G  R  N  F  190

841 AGCTGTGTGTTCTGGAATACTCACGTGAGGGAACTTACTTTGGCCAGCATTGACCTTCAA 900
191 S  C  V  F  W  N  T  H  V  R  E  L  T  L  A  S  I  D  L  Q  210
```

Figure 3B

```
 901  AGTCAGATGGAACCCAGGACCCATCCAACTTGGCTGCTTCACATTTTCATCCCCTCCTGC   960
 211  S  Q  M  E  P  R  T  H  P  T  W  L  L  H  I  F  I  P  S  C     230

 961  ATCATTGCTTTCATTTTCATAGCCACAGTGATAGCCCTAAGAAAACAACTCTGTCAAAAG  1020
 231  I  I  A  F  I  F  I  A  T  V  I  A  L  R  K  Q  L  C  Q  K     250

1021  CTGTATTCTTCAAAAGACACAACAAAAAGACCTGTCACCACAACAAAGAGGGAAGTGAAC  1080
 251  L  Y  S  S  K  D  T  T  K  R  P  V  T  T  T  K  R  E  V  N     270

1081  AGTGCTGTGAATCTGAACCTGTGGTCTTGGGAGCCAGGGTGACCTGATATGACATCTAAA  1140
 271  S  A  V  N  L  N  L  W  S  W  E  P  G  *                       284

1141  GAAGCTTCTGGACTCTGAACAAGAATTCGGTGGCCTGCAGAGCTTGCCATTTGCACTTTT  1200

1201  CAAATGCCTTTGGATGACCCAGCACTTTAATCTGAAACCTGCAACAAGACTAGCCAACAC  1260

1261  CTGGCCATGAAACTTGCCCCTTCACTGATCTGGACTCACCTCTGGAGCCTATGGCTTTAA  1320

1321  GCAAGCACTACTGCACTTTACAGAATTACCCCACTGGATCCTGGACCCACAGAATTCCTT  1380

1381  CAGGATCCTTCTTGCTGCCAGACTGAAAGCAAAAGGAATTATTTCCCCTCAAGTTTTCTA  1440

1441  AGTGATTTCCAAAAGCAGAGGTGTGTGGAAATTTCCAGTAACAGAAACAGATGGGTTGCC  1500

1501  AATAGAGTTATTTTTTATCTATAGCTTCCTCTGGGTACTAGAAGAGGCTATTGAGACTAT  1560

1561  GAGCTCACAGACAGGGCTTCGCACAAACTCAAATCATAATTGACATGTTTTATGGATTAC  1620

1621  TGGAATCTTGATAGCATAATGAAGTTGTTCTAATTAACAGAGAGCATTTAAATATACACT  1680

1681  AAGTGCACAAATTGTGGAGTAAAGTCATCAAGCTCTGTTTTTGAGGTCTAAGTCACAAAG  1740

1741  CATTTGTTTTAACCTGTAATGGCACCATGTTTAATGGTGGTTTTTTTTTTGAACTACATC  1800

1801  TTTCCTTTAAAAATTATTGGTTTCTTTTTATTTGTTTTTACCTTAGAAATCAATTATATA  1860

1861  CAGTCAAAAATATTTGATATGCTCATACGTTGTATCTGCAGCAATTTCAGATAAGTAGCT  1920

1921  AAAATGGCCAAAGCCCCAAACTAAGCCTCCTTTTCTGGCCCTCAATATGACTTTAAATTT  1980
```

Figure 3C

```
1981  GACTTTTCAGTGCCTCAGTTTGCACATCTGTAATACAGCAATGCTAAGTAGTCAAGGCCT  2040

2041  TTGATAATTGGCACTATGGAAATCCTGCAAGATCCCACTACATATGTGTGGAGCAGAAGG  2100

2101  GTAACTCGGCTACAGTAACAGCTTAATTTTGTTAAATTTGTTCTTTATACTGGAGCCATG  2160

2161  AAGCTCAGAGCATTAGCTGACCCTTGAACTATTCAAATGGCACATTAGCTAGTATAACA  2220

2221  GACTTACATAGGTGGGCCTAAAGCAAGCTCCTTAACTGAGCAAAATTTGGGGCTTATGAG  2280

2281  AATGAAAGGGTGTGAAATTGACTAACAGACAAATCATACATCTCAGTTTCTCAATTCTCA  2340

2341  TGTAAATCAGAGAATGCCTTTAAAGAATAAAACTCAATTGTTATTCTTCAAAAAAAAAA  2400

2401  AAAAAA  2406
```

Figure 4

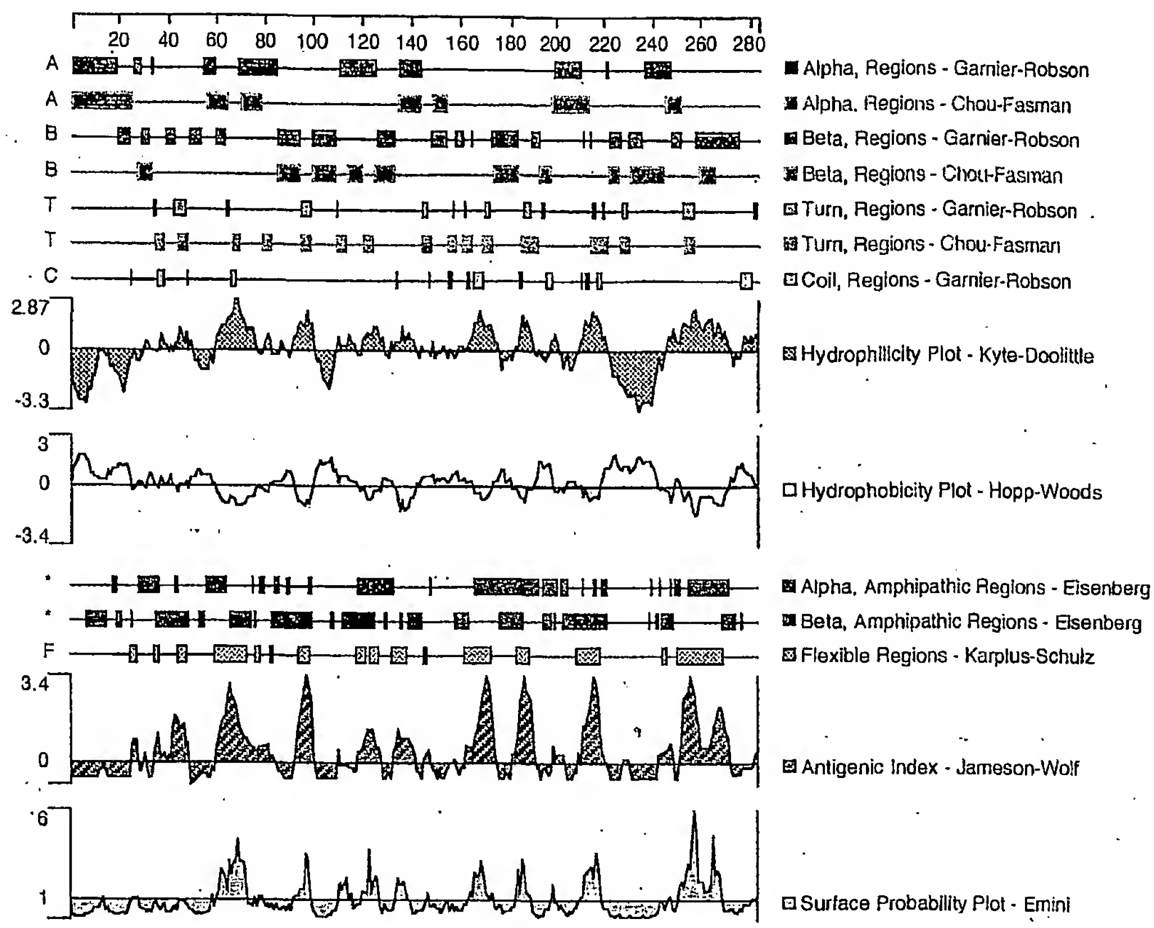

20 40 60 80 100 120 140 160 180 200 220 240 260 280
A
A
B
B
T
T
C
2.87
0
-3.3
3
0
-3.4
F
3.4
0
6
1
Alpha, Regions - Garnier-Robson
Alpha, Regions - Chou-Fasman
Beta, Regions - Garnier-Robson
Beta, Regions - Chou-Fasman
Turn, Regions - Garnier-Robson
Turn, Regions - Chou-Fasman
Coil, Regions - Garnier-Robson
Hydrophilicity Plot - Kyte-Doolittle
Hydrophobicity Plot - Hopp-Woods
Alpha, Amphipathic Regions - Eisenberg
Beta, Amphipathic Regions - Eisenberg
Flexible Regions - Karplus-Schulz
Antigenic Index - Jameson-Wolf
Surface Probability Plot - Emini

Figure 5A

```
  1 GGCACGAGCTGTCATCCGTTTCCATGCCGTGAGGTCCATTCACAGAACACATCCATGGCT  60
  1                                                      M  A    2

 61 CTCATGCTCAGTTTGGTTCTGAGTCTCCTCAAGCTGGGATCAGGGCAGTGGCAGGTGTTT 120
  3 L  M  L  S  L  V  L  S  L  L  K  L  G  S  G  Q  W  Q  V  F   22

121 GGGCCAGACAAGCCTGTCCAGGCCTTGGTGGGGGAGGACGCAGCATTCTCCTGTTTCCTG 180
 23 G  P  D  K  P  V  Q  A  L  V  G  E  D  A  A  F  S  C  F  L   42

181 TCTCCTAAGACCAATGCAGAGGCCATGGAAGTGCGGTTCTTCAGGGGCCAGTTCTCTAGC 240
 43 S  P  K  T  N  A  E  A  M  E  V  R  F  F  R  G  Q  F  S  S   62

241 GTGGTCCACCTCTACAGGGACGGGAAGGACCAGCCATTTATGCAGATGCCACAGTATCAA 300
 63 V  V  H  L  Y  R  D  G  K  D  Q  P  F  M  Q  M  P  Q  Y  Q   82

301 GGCAGGACAAAACTGGTGAAGGATTCTATTGCGGAGGGGCGCATCTCTCTGAGGCTGGAA 360
 83 G  R  T  K  L  V  K  D  S  I  A  E  G  R  I  S  L  R  L  E  102

361 AACATTACTGTGTTGGATGCTGGCCTCTATGGGTGCAGGATTAGTTCCCAGTCTTACTAC 420
103 N  I  T  V  L  D  A  G  L  Y  G  C  R  I  S  S  Q  S  Y  Y  122

421 CAGAAGGCCATCTGGGAGCTACAGGTGTCAGCACTGGGCTCAGTTCCTCTCATTTCCATC 480
123 Q  K  A  I  W  E  L  Q  V  S  A  L  G  S  V  P  L  I  S  I  142

481 GCGGGATATGTTGATAGAGACATCCAGCTACTCTGTCAGTCCTCGGGCTGGTTCCCCCGG 540
143 A  G  Y  V  D  R  D  I  Q  L  L  C  Q  S  S  G  W  F  P  R  162

541 CCCACAGCGAAGTGGAAAGGTCCACAAGGACAGGATTTGTCCACAGACTCCAGGACAAAC 600
163 P  T  A  K  W  K  G  P  Q  G  Q  D  L  S  T  D  S  R  T  N  182

601 AGAGACATGCATGGCCTGTTTGATGTGGAGATCTCTCTGACCGTCCAAGAGAACGCCGGG 660
183 R  D  M  H  G  L  F  D  V  E  I  S  L  T  V  Q  E  N  A  G  202

661 AGCATATCCTGTTCCATGCGGCATGCTCATCTGAGCCGAGAGGTGGAATCCAGGGTACAG 720
203 S  I  S  C  S  M  R  H  A  H  L  S  R  E  V  E  S  R  V  Q  222

721 ATAGGAGACTGGAGAAGAAAGCACGGACAGGCAGGTAAAAGAAAATATTCCTCTTCACAC 780
223 I  G  D  W  R  R  K  H  G  Q  A  G  K  R  K  Y  S  S  S  H  242

781 ATTTATGACTCCTTTCCAAGTCTCTCGTTTATGGATTTTTATATCCTGAGGCCCGTGGGT 840
243 I  Y  D  S  F  P  S  L  S  F  M  D  F  Y  I  L  R  P  V  G  262
```

Figure 5B

```
841  CCCTGCAGAGCCAAGCTTGTGATGGGAACTCTGAAATTGCAGATTCTGGGGGAGGTGCAT  900
263  P  C  R  A  K  L  V  M  G  T  L  K  L  Q  I  L  G  E  V  H   282

901  TTTGTAGAGAAGCCCCATAGCCTTCTTCAGATCTCTGGAGGGTCCACAACACTCAAAAAG  960
283  F  V  E  K  P  H  S  L  L  Q  I  S  G  G  S  T  T  L  K  K   302

961  GGTCCCAATCCTTGGTCTTTCCCTTCTCCCTGCGCCCTGTTTCCCACGTGAGCACGGAAC  1020
303  G  P  N  P  W  S  F  P  S  P  C  A  L  F  P  T  *            319

1021 TGCCTGCTCTCTCTGCTTGCTTTCAGAATTGAGAGACGCCCGGAAACACGCAGGTACCAA  1080

1081 CGCCTGAGAGGGTAACAGTGGGCATGGAGTAGGAAGATGACCAGTGACAGATATGGAGCC  1140

1141 CATCCAGCTTGTAGACAGCAAATCTGTGATGCCCGAATCCACCCCAGGGTGCAGCTGCCT  1200

1201 CTAAATACACTTCTTGGCCCAGGACTTGGAGGGAAAAGCGTAGGGACTGGGTCAGCTAGG  1260

1261 AGGGGTCACAGGCAAGACGCCAGGGAACTGAGGGCATTAGTAGCTGGCTTCTAGGGGTCT  1320

1321 GTGCAAAGGGGAACGAAGTGAAGTTAGCAGGAACTGGTGGGTGGAAGGAAGCTGAATCCT  1380

1381 GGAGTCACTCAAGGTCTCACAAAGTCAAATAGAGGGCTTACGTGGGAGGGCAGTGGTAGG  1440

1441 GCTGGGTGAACATCTCATGGTTGAGCATCTCCAAGCATCAGTGAGGCACGGGGGCTGCCC  1500

1501 TGGAGAAGGTACATGGCTGGTGGGATAGTGGGACTGGCCGGATCCTACCCGGAGCCAGTC  1560

1561 TGCAGTGGGAGGGTCGACCTCTTGCTCCAGCCCAGATTTCGTCTTCAGTAACTCATGCTT  1620

1621 CCTCTCTCCCCCACCGCACCCCAGTGGAGGTGACTCTGGATCCAGAGACGGCTCACCCGA  1680

1681 AGCTCTGCGTTTCTGATCTGAAAACTGTAACCCATAGAAAAGCTCCTCAGGAGGTGCCTC  1740

1741 ACTCTGAGAAGAGATTTACAAGGAAGAGTGTGGTGGCTTCTCAGGGTTTCCAAGCAGGGA  1800

1801 AACATTACTGGGAGGTGGACGTGGGACAAAATGTAGGGTGGTATGTGGGAGTGTGTCGGG  1860

1861 ATGACGTAGACAGGGGGAAGAACAATGTGACTTTGTCTCCCAACAATGGGTATTGGGTCC  1920
```

Figure 5C

1921 TCAGACTGACAACAGAACATTTGTATTTCACATTCAATCCCCATTTTATCAGCCTCCCCC 1980

1981 CCAGCACCCCTCCTACACGAGTAGGGGTCTTCCTGGACTATGAGGGTGGACCATCTCCT 2040

2041 TCTTCAATACAAATGACCAGTCCCTTATTTATACCCTGCTGACATGTCAGTTTGAAGGCT 2100

2101 TGTTGAGACCCTATATCCAGCATGCGATGTATGACGAGGAAAAGGGGACTCCCATATTCA 2160

2161 TATGTCCAGTGTCCTGGGGATGAGACAGAGAAGACCCTGCTTAAAGGGCCCCACACCACA 2220

2221 GACCCAGACACAGCCAAGGGAGAGTGCTCCCGACAGGTGGCCCCAGCTTCCTCTCCGGAG 2280

2281 CCTGCGCACAGAGAGTCACGCCCCCCACTCTCCTTTAGGGAGCTGAGGTTCTTCTGCCCT 2340

2341 GAGCCCTGCAGCAGCGGCAGTCACAGCTTCCAGATGAGGGGGGATTGGCCTGACCCTGTG 2400

2401 GGAGTCAGAAGCCATGGCTGCCCTGAAGTGGGGACGGAATAGACTCACATTAGGTTTAGT 2460

2461 TTGTGAAAACTCCATCCAGCTAAGCGATCTTGAACAAGTCACAACCTCCCAGGCTCCTCA 2520

2521 TTTGCTAGTCACGGACAGTGATTCCTGCCTCACAGGTGAAGATTAAAGAGACAACGAATG 2580

2581 TGAATCATGCTTGCAGGTTTGAGGGCCACAGTGTTTGCTAATGGATGTGTTTTTATGATT 2640

2641 ATACATTTTCCCCACCATAAAACTCTGTTTGCCTTAATTCCCACATTAATTTAACTTTTC 2700

2701 CTCCTATACCCAAATCCACCCATGGAATAGTTAATTGGAACACCTGCCTTTGTGAGGCTC 2760

2761 CAAAGAATAAAGAGGAGGTAGGATTTTTCACTGATTCTATAAGCCCAGCATTACCTGATA 2820

2821 CCAAAACCAGGCAAAGAAAACAGAAGAAGAGGAAGGAAAACTACAGGTCCATATCCCTCA 2880

2881 TTAACACAGACACAAAAATTCTAAATAAAATTTTAACAAATTAAACTAAACAATATATTT 2940

2941 AAAGATGATATATAACTACTCAGTGTGGTTTGTCCCACAAATGCAGAGTTGGTTTAATAT 3000

3001 TTAAATATCAACCAGTGTAATTCAGCACATTAATAAAGTAAAAAAAAAAAAAAAAAAAA 3059

Figure 6

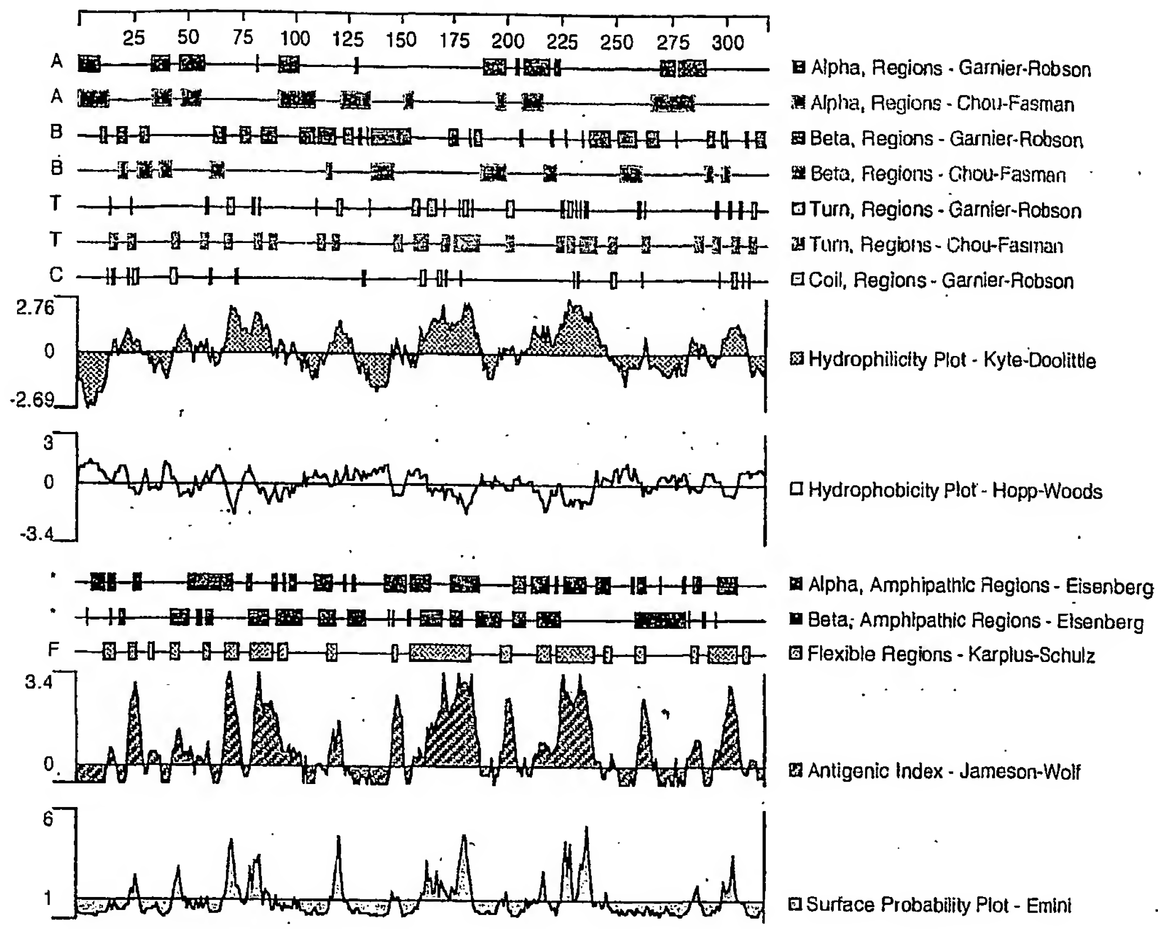

25 50 75 100 125 150 175 200 225 250 275 300
A
A
B
B
T
T
C
Alpha, Regions - Garnier-Robson
Alpha, Regions - Chou-Fasman
Beta, Regions - Garnier-Robson
Beta, Regions - Chou-Fasman
Turn, Regions - Garnier-Robson
Turn, Regions - Chou-Fasman
Coil, Regions - Garnier-Robson
2.76
0
-2.69
Hydrophilicity Plot - Kyte-Doolittle
3
0
-3.4
Hydrophobicity Plot - Hopp-Woods
Alpha, Amphipathic Regions - Eisenberg
Beta, Amphipathic Regions - Eisenberg
F
Flexible Regions - Karplus-Schulz
3.4
0
Antigenic Index - Jameson-Wolf
6
1
Surface Probability Plot - Emini

Figure 7A

```
  1  NNCACGAGCCTGTGCCCCTGGAAAGGTTGGAGACTTGGGGGACGACTGGAGAATTGCCAT   60

 61  TTGAGGACCAAAGGAGAAAAGAAACTACACGCTAATTCTAGAAGGCCTCCTGTCCCTGCC  120

121  TGCTCTGGGTGCTCATGGAACCAGCTGCTGCCCTGCACTTCTCCCGGCCAGCCTCCCTCC  180
  1                M  E  P  A  A  A  L  H  F  S  R  P  A  S  L  L   16

181  TCCTCCTCCTCAGCCTGTGTGCACTGGTCTCAGCCCAGTTTACTGTCGTGGGGCCAGCTA  240
 17   L  L  L  S  L  C  A  L  V  S  A  Q  F  T  V  V  G  P  A  N   36

241  ATCCCATCCTGGCCATGGTGGGAGAAAACACTACATTACGCTGCCATCTGTCACCCGAGA  300
 37   P  I  L  A  M  V  G  E  N  T  T  L  R  C  H  L  S  P  E  K   56

301  AAAATGCTGAGGACATGGAGGTGCGGTGGTTCCGGTCTCAGTTCTCCCCCGCAGTGTTTG  360
 57   N  A  E  D  M  E  V  R  W  F  R  S  Q  F  S  P  A  V  F  V   76

361  TGTATAAGGGTGGGAGAGAGAGAACAGAGGAGCAGATGGAGGAGTACCGGGGAAGAATCA  420
 77   Y  K  G  G  R  E  R  T  E  E  Q  M  E  E  Y  R  G  R  I  T   96

421  CCTTTGTGAGCAAAGACATCAACAGGGGCAGCGTGGCCCTGGTCATACATAACGTCACAG  480
 97   F  V  S  K  D  I  N  R  G  S  V  A  L  V  I  H  N  V  T  A  116

481  CCCAGGAGAATGGGATCTACCGCTGTTACTTCCAAGAAGGCAGGTCCTACGATGAGGCCA  540
117   Q  E  N  G  I  Y  R  C  Y  F  Q  E  G  R  S  Y  D  E  A  I  136

541  TCCTACGCCTCGTGGTGGCAGGCCTTGGGTCTAAGCCCCTCATTGAAATCAAGGCCCAAG  600
137   L  R  L  V  V  A  G  L  G  S  K  P  L  I  E  I  K  A  Q  E  156

601  AGGATGGGAGCATCTGGCTGGAGTGCATATCTGGAGGGTGGTACCCAGAGCCCCTCACAG  660
157   D  G  S  I  W  L  E  C  I  S  G  G  W  Y  P  E  P  L  T  V  176

661  TGTGGAGGGACCCCTACGGTGAGGTTGTGCCCGCCCTGAAGGAGGTTTCCATCGCTGATG  720
177   W  R  D  P  Y  G  E  V  V  P  A  L  K  E  V  S  I  A  D  A  196

721  CTGACGGCCTCTTCATGGTCACCACAGCTGTGATCATCAGAGACAAGTATGTGAGGAATG  780
197   D  G  L  F  M  V  T  T  A  V  I  I  R  D  K  Y  V  R  N  V  216

781  TGTCCTGCTCTGTCAACAACACCCTGCTCGGCCAGGAGAAGGAAACTGTCATTTTTATTC  840
217   S  C  S  V  N  N  T  L  L  G  Q  E  K  E  T  V  I  F  I  P  236

841  CAGAATCCTTTATGCCCAGCGCATCTCCCTGGATGGTGGCCCTAGCTGTCATCCTGACCG  900
237   E  S  F  M  P  S  A  S  P  W  M  V  A  L  A  V  I  L  T  A  256
```

Figure 7B

```
 901  CATCTCCCTGGATGGTGTCCATGACTGTCATCCTGGCTGTTTTCATCATCTTCATGGCTG   960
 257   S  P  W  M  V  S  M  T  V  I  L  A  V  F  I  I  F  M  A  V   276

 961  TCAGCATCTGTTGCATCAAGAAACTTCAAAGGGAAAAAAAGATTCTGTCAGGGGAAAAGA  1020
 277   S  I  C  C  I  K  K  L  Q  R  E  K  K  I  L  S  G  E  K  K   296

1021  AAGTTGAACAAGAGGAAAAAGAAATTGCACAGCAACTTCAAGAAGAATTGCGATGGAGAA  1080
 297   V  E  Q  E  E  K  E  I  A  Q  Q  L  Q  E  E  L  R  W  R  R   316

1081  GAACATTCTTACATGCTGCTGATGTGGTCCTGGATCCAGACACCGCTCATCCCGAGCTCT  1140
 317   T  F  L  H  A  A  D  V  V  L  D  P  D  T  A  H  P  E  L  F   336

1141  TCCTGTCAGAGGACCGGAGAAGTGTGAGGCGGGGCCCCTACAGGCAGAGAGTGCCTGACA  1200
 337   L  S  E  D  R  R  S  V  R  R  G  P  Y  R  Q  R  V  P  D  N   356

1201  ACCCAGAGAGATTCGACAGTCAGCCTTGTGTCCTGGGATGGGAGAGCTTCGCCTCAGGGA  1260
 357   P  E  R  F  D  S  Q  P  C  V  L  G  W  E  S  F  A  S  G  K   376

1261  AACATTACAGGGGAAACTTCACAGAGTGGGGACCCACCAGAGCCTATAGAATCAATTCCT  1320
 377   H  Y  R  G  N  F  T  E  W  G  P  T  R  A  Y  R  I  N  S  L   396

1321  TGGACTCACAGCCATGCAGAAAGCCCTGGCCATCTCAGCAGCCACCGCACAACCCCCCTA  1380
 397   D  S  Q  P  C  R  K  P  W  P  S  Q  Q  P  P  H  N  P  P  N   416

1381  ATGAAAGACACGCCCTCCTCCCCTCTGGTCACGTAAGAGAACATCTTCCAGCTGCCTTTT  1440
 417   E  R  H  A  L  L  P  S  G  H  V  R  E  H  L  P  A  A  F  F   436

1441  TCACACCCACTCCAGCCCTCTGCCCCAGTTTTCTCCTCCTCACTAGTCTGTGGCTTTAGT  1500
 437   T  P  T  P  A  L  C  P  S  F  L  L  L  T  S  L  W  L  *      455

1501  AGTTCCTTTGCTTGTAATTATGGGATGGGATCCAGGCATAGGGAACTAGTTGTTTCATAG  1560

1561  CTCCCAGTCAAAAAGAAAGTGAGAGAAGCTGTTGGGCAGCGAACCTACTGTTTAAAATCA  1620

1621  GGATAACCACATTAAGCCCAATATGCCAGTTGGCACCAGATGCTGTGGACTTGGAATGAG  1680

1681  GCCAACAGGGTTCACCAGGATGAGAGAGGAGAGAGGAATCCACAGGACCACCAGAAGGGA  1740

1741  GAGGGAACCAGATATGCAGATCAGAGATAGAGGAAGTGTTGAGAGGAAAGGGGAGGTCCT  1800

1801  GCTGATTCCTCAGAATGGCTTCTGGACCCTGGAGATGTTTGGAAACCAATACCGGGCCCT  1860
```

Figure 7C

```
1861  GTCCTCCCCTGAGAGGATTCTCCCTTTGAAGGAGTCCCTTTGCCGGGTGGCGTCTTCCT  1920

1921  GGACTATGAAGCTGGAGATGTCTCCTTCTACAACATGAGGGACAGATCACACATCTACAC  1980

1981  ATGTCCCCGTTCAGCCTTTAATGTGCCTGTGAGGCCATTCTTCAGGTTAGGGTCTGATGA  2040

2041  CAGCCCCATCTTCATCTGCCCTGCACTCACAGGAGCCAGTGGGGTCATGGTGCCTGAAGA  2100

2101  GGGCCTGAAACTTCACAGAGTGGGGACCCACCAAGGTTGTAAGGATGGCTAAGTCCCACC  2160

2161  ATAAGAGCTAAAGGGTCCTGGGAGATGATGGCTCATTTCCACCCAACCCCAGGATTTCCA  2220

2221  CAGCACACACCCACAGGCCTGGACCTGGGATGAAGATGAATGAAGAACATGGACTCATGT  2280

2281  GGATGTGGTTTGGCTCAGATGTCCCTGCAATAAACAAGGGGTCAGTACTTAGTCCCTGAG  2340

2341  TGTGGTTGAGGTTTGAGGTCCTGGTCGAGCAGGGCAGTACTGGACCAGGTCTACGTCAGC  2400

2401  ATTCAGGTTCAATGGGGACACCAGTGGCTTCAAACTTCCTGATCTAATTATGTTTTTAGA  2460

2461  CACTTAGAAGTTATTGAGGACTTTAAAGAACTTTTGTTTATTTGGGTTAATATTTATGAC  2520

2521  ATTTGACCATTGAAACAAAAATTTAAAATGTTATCTTTTAATTTATGTTAAAATAGCATT  2580

2581  AATAAATCAGTTATAGGTTAATGTAGATAGGATGTTTTGTGAAAAAGCAATCTATTGTGT  2640

2641  CCAAATAAAAAAACAAAAAGTGTAAAAAAAAAAAAAAAAAAA  2682
```

Figure 8

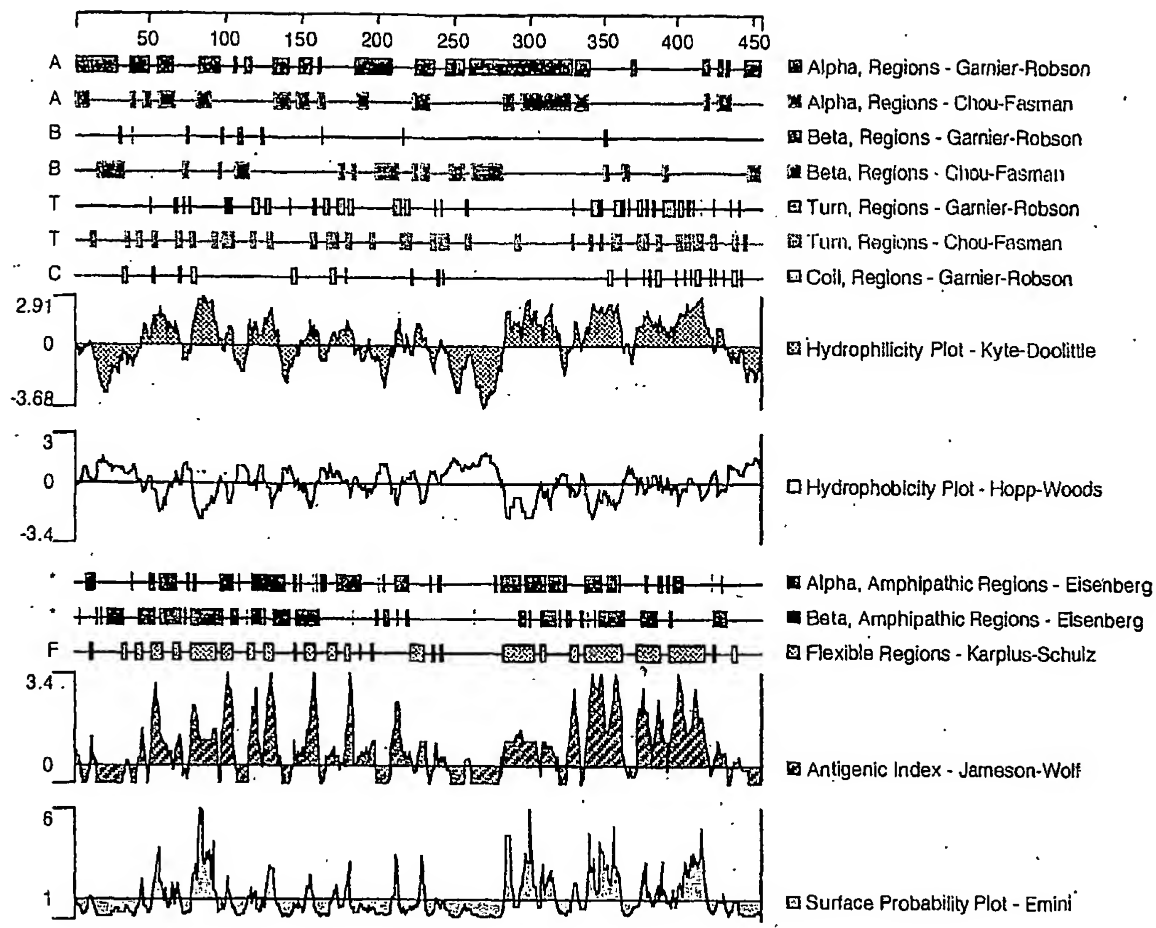

50
100
150
200
250
300
350
400
450
A
A
B
B
T
T
C
2.91
0
-3.68
3
0
-3.4
F
3.4
0
6
1
Alpha, Regions - Garnier-Robson
Alpha, Regions - Chou-Fasman
Beta, Regions - Garnier-Robson
Beta, Regions - Chou-Fasman
Turn, Regions - Garnier-Robson
Turn, Regions - Chou-Fasman
Coil, Regions - Garnier-Robson
Hydrophilicity Plot - Kyte-Doolittle
Hydrophobicity Plot - Hopp-Woods
Alpha, Amphipathic Regions - Eisenberg
Beta, Amphipathic Regions - Eisenberg
Flexible Regions - Karplus-Schulz
Antigenic Index - Jameson-Wolf
Surface Probability Plot - Emini

Figure 9A

```
  1  CGATTCGGCTCCAAACTCCGGCGCTGCAGCCGATCGGACTCTGGGCCGCGGTGGGCACCG   60

 61  CGCGCAGCTAGGGAGCCGAGAACCGCGGCGAGCCCCGAGGACGCCCAGAGCGCGAGGGTC  120

121  GCTGCGCCTCGCAGAGCCGGAGCCGAGTCGAGCCGGGCGCCCGGGCTGCCTGGAGACGCC  180

181  GTGACTTTGAAGTGTAACTTCAAGACAGATGGGCGCATGCGGGAGATCGTGTGGTACCGG  240
  1                                    M  R  E  I  V  W  Y  R      8

241  GTGACGGATGGTGGCACCATCAAGCAAAAGATCTTCACCTTCGACGCCATGTTCTCCACC  300
  9  V  T  D  G  G  T  I  K  Q  K  I  F  T  F  D  A  M  F  S  T     28

301  AACTACTCACACATGGAGAACTACCGCAAGCGAGAGGACCTGGTGTACCAGTCCACTGTG  360
 29  N  Y  S  H  M  E  N  Y  R  K  R  E  D  L  V  Y  Q  S  T  V     48

361  AGGCTGCCCGAGGTCCGGATCTCAGACAATGGTCCCTATGAGTGCCATGTGGGCATCTAC  420
 49  R  L  P  E  V  R  I  S  D  N  G  P  Y  E  C  H  V  G  I  Y     68

421  GACCGCGCCACCAGGGAGAAGGTGGTCCTGGCATCAGGCAACATCTTCCTCAACGTCATG  480
 69  D  R  A  T  R  E  K  V  V  L  A  S  G  N  I  F  L  N  V  M     88

481  GCTCCTCCCACCTCCATTGAAGTGGTGGCTGCTGACACACCAGCCCCCTTCAGCCGCTAC  540
 89  A  P  P  T  S  I  E  V  V  A  A  D  T  P  A  P  F  S  R  Y    108

541  CAAGCCCAGAACTTCACGCTGGTCTGCATCGTGTCTGGAGGAAAACCAGCACCCATGGTT  600
109  Q  A  Q  N  F  T  L  V  C  I  V  S  G  G  K  P  A  P  M  V    128

601  TATTTCAAACGAGATGGGGAACCAATCGACGCAGTGCCCCTATCAGAGCCACCAGCTGCG  660
129  Y  F  K  R  D  G  E  P  I  D  A  V  P  L  S  E  P  P  A  A    148

661  AGCTCCGGCCCCCTACAGGACAGCAGGCCCTTCCGCAGCCTTCTGCACCGTGACCTGGAT  720
149  S  S  G  P  L  Q  D  S  R  P  F  R  S  L  L  H  R  D  L  D    168

721  GACACCAAGATGCAGAAGTCACTGTCCCTCCTGGACGCCGAGAACCGGGGTGGGCGACCC  780
169  D  T  K  M  Q  K  S  L  S  L  L  D  A  E  N  R  G  G  R  P    188

781  TACACGGAGCGCCCCTCCCGTGGCCTGACCCCAGATCCCAACATCCTCCTCCAGCCAACC  840
189  Y  T  E  R  P  S  R  G  L  T  P  D  P  N  I  L  L  Q  P  T    208

841  ACAGAGAACATACCAGAGACGGTCGTGAGCCGTGAGTTTCCCCGCTGGGTCCACAGCGCC  900
209  T  E  N  I  P  E  T  V  V  S  R  E  F  P  R  W  V  H  S  A    228
```

Figure 9B

```
 901  GAGCCCACCTACTTCCTGCGCCACAGCCGCACCCCGAGCAGTGACGGCACTGTGGAAGTA   960
 229  E  P  T  Y  F  L  R  H  S  R  T  P  S  S  D  G  T  V  E  V     248

 961  CGTGCCCTGCTCACCTGGACCCTCAACCCACAGATCGACAACGAGGCCCTCTTCAGCTGC   1020
 249  R  A  L  L  T  W  T  L  N  P  Q  I  D  N  E  A  L  F  S  C     268

1021  GAGGTCAAGCACCCAGCTCTGTCGATGCCCATGCAGGCAGAGGTCACGCTGGTTGCCCCC   1080
 269  E  V  K  H  P  A  L  S  M  P  M  Q  A  E  V  T  L  V  A  P     288

1081  AAAGGACCCAAAATTGTGATGACGCCCAGCAGAGCCCGGGTAGGGGACACAGTGAGGATT   1140
 289  K  G  P  K  I  V  M  T  P  S  R  A  R  V  G  D  T  V  R  I     308

1141  CTGGTCCATGGGTTTCAGAACGAAGTCTTCCCGGAGCCCATGTTCACGTGGACGCGGGTT   1200
 309  L  V  H  G  F  Q  N  E  V  F  P  E  P  M  F  T  W  T  R  V     328

1201  GGGAGCCGCCTCCTGGACGGCAGCGCTGAGTTCGACGGGAAGGAGCTGGTGCTGGAGCGG   1260
 329  G  S  R  L  L  D  G  S  A  E  F  D  G  K  E  L  V  L  E  R     348

1261  GTTCCCGCCGAGCTCAATGGCTCCATGTATCGCTGCACCGCCCAGAACCCACTGGGCTCC   1320
 349  V  P  A  E  L  N  G  S  M  Y  R  C  T  A  Q  N  P  L  G  S     368

1321  ACCGACACGCACACCCGGCTCATCGTGTTTGAAAACCCAAATATCCCAAGAGGAACGGAG   1380
 369  T  D  T  H  T  R  L  I  V  F  E  N  P  N  I  P  R  G  T  E     388

1381  GACTCTAATGGTTCCATTGGCCCCACTGGTGCCCGGCTCACCTTGGTGCTCGCCCTGACA   1440
 389  D  S  N  G  S  I  G  P  T  G  A  R  L  T  L  V  L  A  L  T     408

1441  GTGATTCTGGAGCTGACGTGAAGGCACCCGCCCCGGCCACTCCATCAGGCACTGACATCT   1500
 409  V  I  L  E  L  T  *                                            415

1501  CCGCGACCGGTTTTCATTTCTTTTCTAAACTATTTCCAGTCTTGTTCTTAGTCTCTTTCC   1560

1561  ATCTGTGTCTTGGCTTCTTCAGTCGGTTTAATTAAAACAAACAGAACAATTTTCCCCACA   1620

1621  AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA   1680

1681  AAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA   1724
```

Figure 10

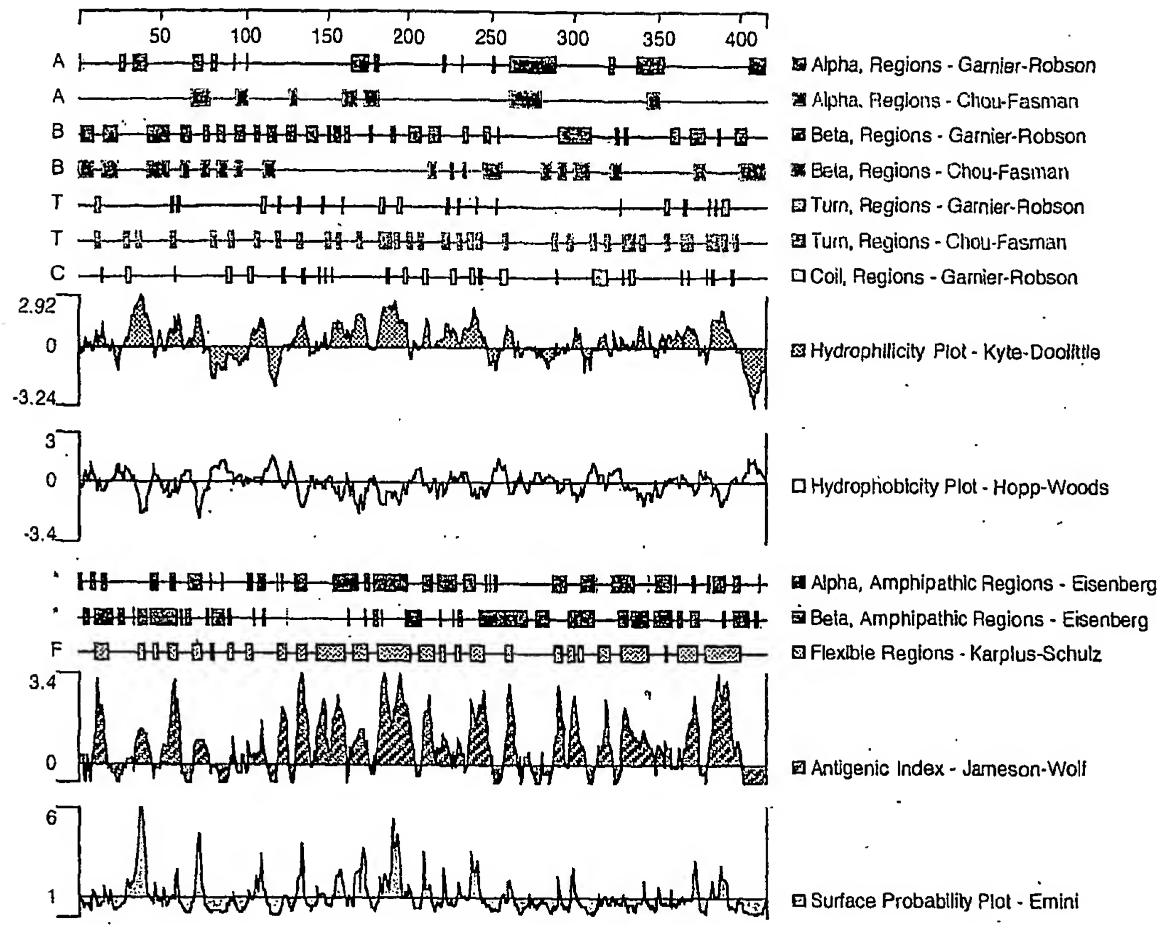

50
100
150
200
250
300
350
400
A
A
B
B
T
T
C
Alpha, Regions - Garnier-Robson
Alpha, Regions - Chou-Fasman
Beta, Regions - Garnier-Robson
Beta, Regions - Chou-Fasman
Turn, Regions - Garnier-Robson
Turn, Regions - Chou-Fasman
Coil, Regions - Garnier-Robson
2.92
0
-3.24
Hydrophilicity Plot - Kyte-Doolittle
3
0
-3.4
Hydrophobicity Plot - Hopp-Woods
Alpha, Amphipathic Regions - Eisenberg
Beta, Amphipathic Regions - Eisenberg
F
Flexible Regions - Karplus-Schulz
3.4
0
Antigenic Index - Jameson-Wolf
6
1
Surface Probability Plot - Emini

Figure 11A

1 CACGAGCCTGTGCCCCTGGAAAGGTTGGAGACTTGGGGGACGACTGGAGAATTGCCATTT 60

61 GAGGACCAAAGGAGAAAAGAAACTACACGCTAATTCTAGAAGGCCTCCTGTCCCTGCCTG 120

121 CTCTGGGTGCTCATGGAACCAGCTGCTGCCCTGCACTTCTCCCGGCCAGCCTCCCTCCTC 180
1 M E P A A A L H F S R P A S L L 16

181 CTCCTCCTCAGCCTGTGTGCACTGGTCTCAGCCCAGGTCACTGTCGTGGGGCCCACTGAT 240
17 L L L S L C A L V S A Q V T V V G P T D 36

241 CCCATCCTGGCCATGGTGGGAGAAAACACTACGTTACGATGCTGTCTGTCACCCGAGGAA 300
37 P I L A M V G E N T T L R C C L S P E E 56

301 AATGCTGAGGACATGGAGGTGCGGTGGTTCCAGTCTCAGTTCTCCCCTGCAGTGTTTGTG 360
57 N A E D M E V R W F Q S Q F S P A V F V 76

361 TATAAGGGTGGAAGAGAGAGAACAGAGGAGCAGAAGGAGGAGTACCGAGGGAGAACCACC 420
77 Y K G G R E R T E E Q K E E Y R G R T T 96

421 TTTGTGAGCAAAGACAGCAGGGGCAGCGTGGCCCTGATCATACACAATGTCACAGCCGAG 480
97 F V S K D S R G S V A L I I H N V T A E 116

481 GATAACGGCATCTACCAGTGTTACTTCCAAGAAGGCAGGTCCTGCAATGAGGCCATCCTG 540
117 D N G I Y Q C Y F Q E G R S C N E A I L 136

541 CACCTTGTGGTGGCAGACCAGCACAATCCTCTTTCCTGGATCCCCATTCCGCAGGGGACA 600
137 H L V V A D Q H N P L S W I P I P Q G T 156

601 CTCTCCCTATGAAAAGAAGATTCCAGGGGAAAAATCCTTCCTCCTGCACAAGGGCCACCA 660
157 L S L * 160

661 TGAGTGAGTTTGCCCTGCTAAGCCGTGGGCTTGACTTCTTGAGAAGCACATGCAGAACTC 720

721 AGTTGAGGCCATGAGCCGGGGGAAAATGGTGAATCTCGGAAGAGAAGTCCTATGCCTGCC 780

781 TTAGCACTGAGCTGTGCACTTCTGAGAGTGAGAGGAGACACCATCAATAATTGTCTTGGG 840

841 ACAACTGGAATAAACAGTGACTGCCCAGAGAACTACGATATTTGAAATCTTATTTCTTGA 900

901 TGAATATTCATCCTGACTTCTTTCCTGAAATGCTGTTTGCAAAGAGAGTGACTTATATGT 960

Figure 11B

961 AAGTAGAGCGTTTTATTAAAGCAAGACTTAATACAGAAGCAAAAAAAAAAAAAAAAAAA 1019

Figure 12

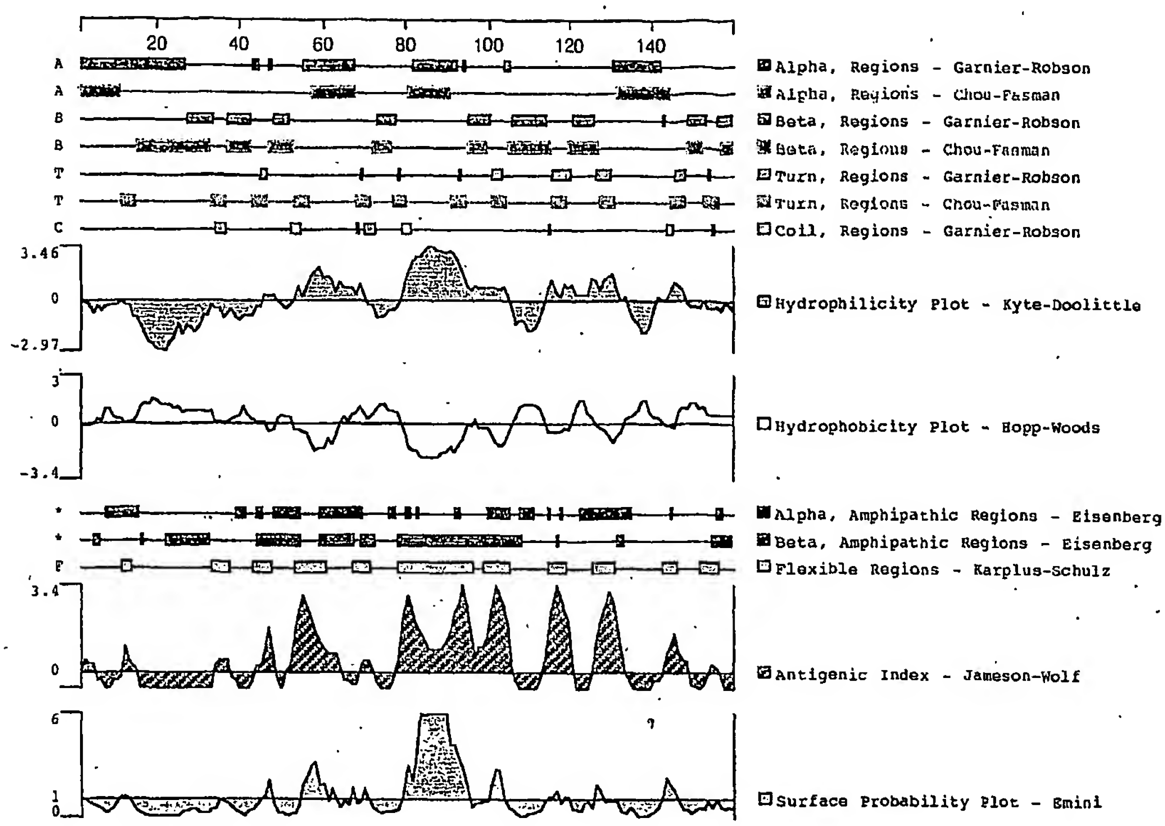

20
40
60
80
100
120
140
A
A
B
B
T
T
C
Alpha, Regions - Garnier-Robson
Alpha, Regions - Chou-Fasman
Beta, Regions - Garnier-Robson
Beta, Regions - Chou-Fasman
Turn, Regions - Garnier-Robson
Turn, Regions - Chou-Fasman
Coil, Regions - Garnier-Robson
3.46
0
-2.97
Hydrophilicity Plot - Kyte-Doolittle
3
0
-3.4
Hydrophobicity Plot - Hopp-Woods
Alpha, Amphipathic Regions - Eisenberg
Beta, Amphipathic Regions - Eisenberg
F
Flexible Regions - Karplus-Schulz
3.4
0
Antigenic Index - Jameson-Wolf
6
1
0
Surface Probability Plot - Emini

Figure 13A

1 ACATCCATGGCTCTAATGCTCAGTTTGGTTCTGAGTCTCCTCAAGCTGGGATCAGGGCAG 60

1 M A L M L S L V L S L L K L G S G Q 18

61 TGGCAGGTGTTTGGGCCAGACAAGCCTGTCCAGGCCTTGGTGGGGGAGGACGCAGCATTC 120

19 W Q V F G P D K P V Q A L V G E D A A F 38

121 TCCTGTTTCCTGTCTCCTAAGACCAATGCAGAGGCCATGGAAGTGCGGTTCTTCAGGGGC 180

39 S C F L S P K T N A E A M E V R F F R G 58

181 CAGTTCTCTAGCGTGGTCCACCTCTACAGGGACGGGAAGGACCAGCCATTTATGCAGATG 240

59 Q F S S V V H L Y R D G K D Q P F M Q M 78

241 CCACAGTATCAAGGCAGGACAAAACTGGTGAAGGATTCTATTGCGGAGGGGCGCATCTCT 300

79 P Q Y Q G R T K L V K D S I A E G R I S 98

301 CTGAGGCTGGAAAACATTACTGTGTTGGATGCTGGCCTCTATGGGTGCAGGATTAGTTCC 360

99 L R L E N I T V L D A G L Y G C R I S S 118

361 CAGTCTTACTACCAGAAGGCCATCTGGGAGCTACAGGTGTCAGCACTGGGCTCAGTTCCT 420

119 Q S Y Y Q K A I W E L Q V S A L G S V P 138

421 CTCATTTCCATCACGGGATATGTTGATAGAGACATCCAGCTACTCTGTCAGTCCTCGGGC 480

139 L I S I T G Y V D R D I Q L L C Q S S G 158

481 TGGTTCCCCCGGCCCACAGCGAAGTGGAAAGGTCCACAAGGACAGGATTTGTCCACAGAC 540

159 W F P R P T A K W K G P Q G Q D L S T D 178

541 TCCAGGACAAACAGAGACATGCATGGCCTGTTTGATGTGGAGATCTCTCTGACCGTCCAA 600

179 S R T N R D M H G L F D V E I S L T V Q 198

601 GAGAACGCCGGGAGCATATCCTGTTCCATGCGGCATGCTCATCTGAGCCGAGAGGTGGAA 660

199 E N A G S I S C S M R H A H L S R E V E 218

661 TCCAGGGTACAGATAGGAGATACCTTTTTCGAGCCTATATCGTGGCACCTGGCTACCAAA 720

219 S R V Q I G D T F F E P I S W H L A T K 238

721 GTACTGGGAATACTCTGCTGTGGCCTATTTTTTGGCATTGTTGGACTGAAGATTTTCTTC 780

239 V L G I L C C G L F F G I V G L K I F F 258

781 TCCAAATTCCAGTGGAAAATCCAGGCGGAACTGGACTGGAGAAGAAAGCACGGACAGGCA 840

259 S K F Q W K I Q A E L D W R R K H G Q A 278

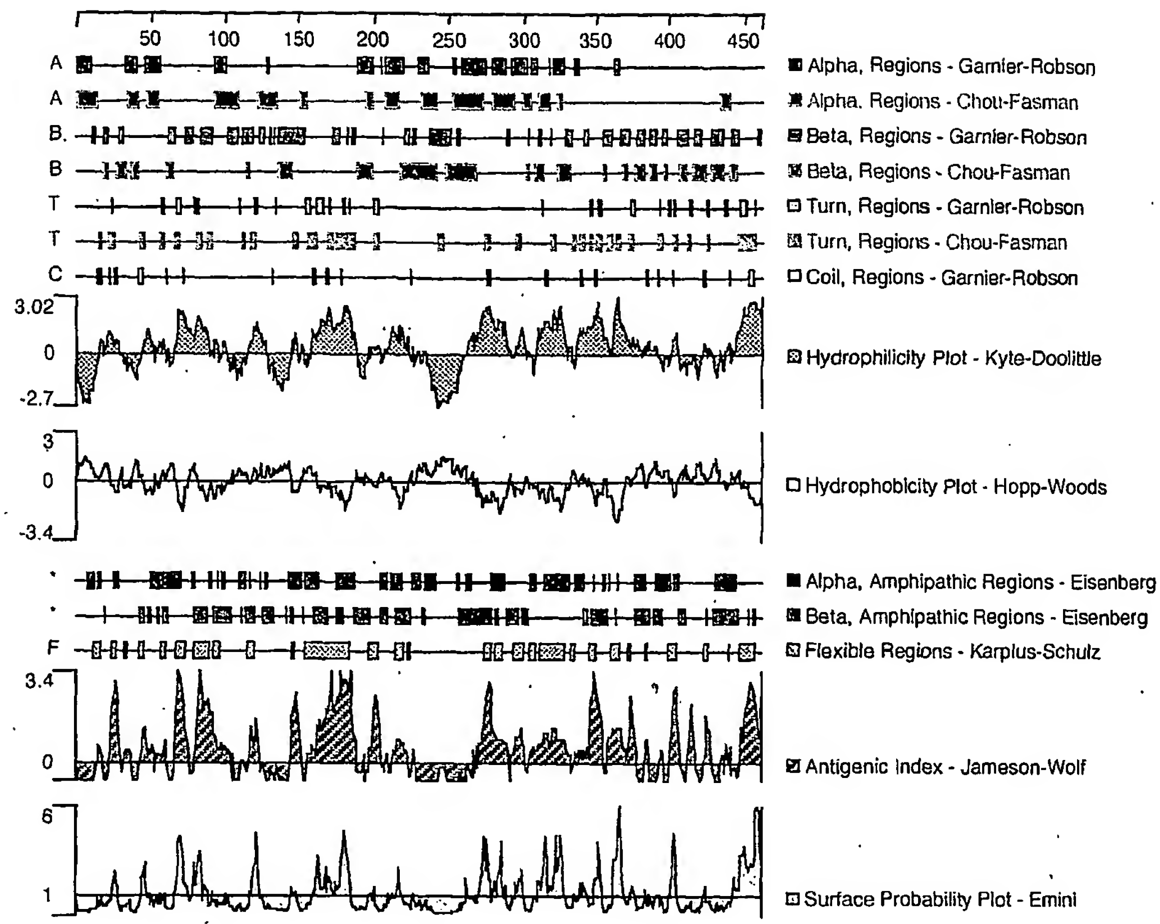
Figure 13B

```
 841 GAATTGAGAGACGCCCGGAAACACGCAGTGGAGGTGACTCTGGATCCAGAGACGGCTCAC  900
 279 E  L  R  D  A  R  K  H  A  V  E  V  T  L  D  P  E  T  A  H   298

 901 CCGAAGCTCTGCGTTTCTGATCTGAAAACTGTAACCCATAGAAAAGCTCCCCAGGAGGTG  960
 299 P  K  L  C  V  S  D  L  K  T  V  T  H  R  K  A  P  Q  E  V   318

 961 CCTCACTCTGAGAAGAGATTTACAAGGAAGAGTGTGGTGGCTTCTCAGAGTTTCCAAGCA  1020
 319 P  H  S  E  K  R  F  T  R  K  S  V  V  A  S  Q  S  F  Q  A   338

1021 GGGAAACATTACTGGGAGGTGGACGGAGGACACAATAAAAGGTGGCGCGTGGGAGTGTGC  1080
 339 G  K  H  Y  W  E  V  D  G  G  H  N  K  R  W  R  V  G  V  C   358

1081 CGGGATGATGTGGACAGGAGGAAGGAGTACGTGACTTTGTCTCCCGATCATGGGTACTGG  1140
 359 R  D  D  V  D  R  R  K  E  Y  V  T  L  S  P  D  H  G  Y  W   378

1141 GTCCTCAGACTGAATGGAGAACATTTGTATTTCACATTAAATCCCCGTTTTATCAGCGTC  1200
 379 V  L  R  L  N  G  E  H  L  Y  F  T  L  N  P  R  F  I  S  V   398

1201 TTCCCCAGGACCCCACCTACAAAAATAGGGGTCTTCCTGGACTATGAGTGTGGGACCATC  1260
 399 F  P  R  T  P  P  T  K  I  G  V  F  L  D  Y  E  C  G  T  I   418

1261 TCCTTCTTCAACATAAATGACCAGTCCCTTATTTATACCCTGACATGTCGGTTTGAAGGC  1320
 419 S  F  F  N  I  N  D  Q  S  L  I  Y  T  L  T  C  R  F  E  G   438

1321 TTATTGAGGCCCTACATTGAGTATCCGTCCTATAATGAGCAAAATGGAACTCCCAGAGAC  1380
 439 L  L  R  P  Y  I  E  Y  P  S  Y  N  E  Q  N  G  T  P  R  D   458

1381 AAGCAACAGTGAGTCCTCCTCACAGGCAACCACGCCCTTCCTCCCCAGGGGTGAAATGTA  1440
 459 K  Q  Q  *                                                   462

1441 GGATGAATCACATCCCACATTCTTCTTTAGGGATATTAAGGTCTCTCTCCCAGATCCAAA  1500

1501 GTCCCGCAGCAGCCGGCCAAGGTGGCTTCCAGATGAAGGGGGACTGGCCTGTCCACATGG  1560

1561 GAGTCAGGTGTCATGGCTGCCCTGAGCTGGGAGGGAAGAAGGCTGACATTACATTTAGTT  1620

1621 TGCTCTCACTCCATCTGGCTAAGTGATCTTGAAATACCACCTCTCAGGTGAAGAACCGTC  1680

1681 AGGAATTCCCATCTCACAGGCTGTGGTGTAGATTAAGTAGACAAGGAATGTGAATAATGC  1740

1741 TTAGATCTTATTGATGACAGAGTGTATCCTAATGGTTTGTTCATTATATTACACTTTCAG  1800
```

Figure 13C

```
1801  TAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA  1833
```

Figure 14



50 100 150 200 250 300 350 400 450
A
A
B.
B
T
T
C
3.02
0
-2.7
3
0
-3.4
F
3.4
0
6
1
Alpha, Regions - Garnier-Robson
Alpha, Regions - Chou-Fasman
Beta, Regions - Garnier-Robson
Beta, Regions - Chou-Fasman
Turn, Regions - Garnier-Robson
Turn, Regions - Chou-Fasman
Coil, Regions - Garnier-Robson
Hydrophilicity Plot - Kyte-Doolittle
Hydrophobicity Plot - Hopp-Woods
Alpha, Amphipathic Regions - Eisenberg
Beta, Amphipathic Regions - Eisenberg
Flexible Regions - Karplus-Schulz
Antigenic Index - Jameson-Wolf
Surface Probability Plot - Emini

<110> Human Genome Sciences, Inc.

<120> B7-Like Polynucleotides, Polypeptides, and Antibodies

<130> PT124PCT

<140> Unassigned
<141> 2001-06-29

<150> 60/215,135
<151> 2000-06-30

<150> 60/225,266
<151> 2000-08-14

<160> 49

<170> PatentIn Ver. 2.0

<210> 1
<211> 733
<212> DNA
<213> Homo sapiens

<400> 1
```
gggatccgga gcccaaatct tctgacaaaa ctcacacatg cccaccgtgc ccagcacctg      60
aattcgaggg tgcaccgtca gtcttcctct tccccccaaa acccaaggac accctcatga     120
tctcccggac tcctgaggtc acatgcgtgg tggtggacgt aagccacgaa gaccctgagg     180
tcaagttcaa ctggtacgtg gacggcgtgg aggtgcataa tgccaagaca aagccgcggg     240
aggagcagta caacagcacg taccgtgtgg tcagcgtcct caccgtcctg caccaggact     300
ggctgaatgg caaggagtac aagtgcaagg tctccaacaa agccctccca acccccatcg     360
agaaaaccat ctccaaagcc aaagggcagc cccgagaacc acaggtgtac accctgcccc     420
catcccggga tgagctgacc aagaaccagg tcagcctgac ctgcctggtc aaaggcttct     480
atccaagcga catcgccgtg gagtgggaga gcaatgggca gccggagaac aactacaaga     540
ccacgcctcc cgtgctggac tccgacggct ccttcttcct ctacagcaag ctcaccgtgg     600
acaagagcag gtggcagcag gggaacgtct tctcatgctc cgtgatgcat gaggctctgc     660
acaaccacta cacgcagaag agcctctccc tgtctccggg taaatgagtg cgacggccgc     720
gactctagag gat                                                        733
```

<210> 2
<211> 3357
<212> DNA
<213> Homo sapiens

<400> 2
```
caccagcagt agtagcagaa gcgaagagcg caaacgcaac cgctctcccc gcgcgttggc      60
cgattcatta atgcagctgg cacgacaggt ttcccgactg gaaagcgggc agtgagcgca     120
acgcaattaa tgtgagttag ctcactcatt aggcacccca ggctttacac tttatgcttc     180
cggctcgtat gttgtgtgga attgtgagcg gataacaatt tcacacagga aacagctatg     240
accatgatta cgccaagctc gaaattaacc ctcactaaag ggaacaaaag ctggagctcc     300
accgcggtgg cggccgctct agaactagtg gatcccccgg gctgcaggaa ttcggcacga     360
gaggcagcgg cagctccact cagccagtac ccagatacgc tgggaacctt ccccagccat     420
ggcttccctg ggcagatcc tcttctggag cataattagc atcatcatta ttctggctgg     480
agcaattgca ctcatcattg gctttggtat ttcagggaga cactccatca cagtcactac     540
tgtcgcctca gctgggaaca ttggggagga tggaatcctg agctgcactt ttgaacctga     600
catcaaactt tctgatatcg tgatacaatg gctgaaggaa ggtgttttag gcttggtcca     660
tgagttcaaa gaaggcaaag atgagctgtc ggagcaggat gaaatgttca gaggccggac     720
agcagtgttt gctgatcaag tgatagttgg caatgcctct ttgcggctga aaaacgtgca     780
```

```
actcacagat gctggcacct acaaatgtta tatcatcact tctaaaggca aggggaatgc    840
taaccttgag tataaaactg gagccttcag catgccggaa gtgaatgtgg actataatgc    900
cagctcagag accttgcggt gtgaggctcc ccgatggttc ccccagccca cagtggtctg    960
ggcatcccaa gttgaccagg gagccaactt ctcggaagtc tccaatacca gctttgagct   1020
gaactctgag aatgtgacca tgaaggttgt gtctgtgctc tacaatgtta cgatcaacaa   1080
cacatactcc tgtatgattg aaaatgacat tgccaaagca acaggggata tcaaagtgac   1140
agaatcggag atcaaaaggc ggagtcacct acagctgcta aactcaaagg cttctctgtg   1200
tgtctcttct ttctttgcca tcagctgggc acttctgcct ctcagccctt acctgatgct   1260
aaaataatgt gccttggcca caaaaaagca tgcaaagtca ttgttacaac agggatctac   1320
agaactattt caccaccaga tatgacctag ttttatattt ctgggaggaa atgaattcat   1380
atctagaagt ctggagtgag caaacaagag caagaaacaa aaagaagcca aagcagaag    1440
gctccaatat gaacaagata aatctatctt caaagacata ttagaagttg ggaaaataat   1500
tcatgtgaac tagacaagtg tgttaagagt gataagtaaa atgcacgtgg agacaagtgc   1560
atccccagat ctcagggacc tccccctgcc tgtcacctgg ggagtgagag gacaggatag   1620
tgcatgttct ttgtctctga atttttagtt atatgtgctg taatgttgct ctgaggaagc   1680
ccctggaaag tctatcccaa catatccaca tcttatattc cacaaattaa gctgtagtat   1740
gtaccctaag acgctgctaa tcgactgcca cttcgcaact caggggcggc tgcattttag   1800
taatgggtca aatgattcac tttttatgat gcttccaaag gtgccttggc ttctcttccc   1860
aactgacaaa tgccaaagtt gagaaaaatg atcataattt tagcataaac agagcagtcg   1920
gcgacaccga ttttataaat aaactgagca ccttcttttt aaacaaacaa atgcgggttt   1980
atttctcaga tgatgttcat ccgtgaatgg tccagggaag gacctttcac cttgactata   2040
tggcattatg tcatcacaag ctctgaggct tctcctttcc atcctgcgtg gacagctaag   2100
acctcagttt tcaatagcat ctagagcagt gggactcagc tggggtgatt tcgcccccca   2160
tctccggggg aatgtctgaa gacaattttg gttacctcaa tgagggagtg gaggaggata   2220
cagtgctact accaactagt ggataaaggc cagggatgct gctcaacctc ctaccatgta   2280
caggacgtct ccccattaca actacccaat ccgaagtgtc aactgtgtca ggactaagaa   2340
accctggttt tgagtagaaa agggcctgga aagaggggag ccaacaaatc tgtctgcttc   2400
ctcacattag tcattggcaa ataagcattc tgtctctttg gctgctgcct cagcacagag   2460
agccagaact ctatcgggca ccaggataac atctctcagt gaacagagtt gacaaggcct   2520
atgggaaatg cctgatggga ttatcttcag cttgttgagc ttctaagttt ctttcccttc   2580
attctaccct gcaagccaag ttctgtaaga gaaatgcctg agttctagct caggttttct   2640
tactctgaat ttagatctcc agaccccttcc tggccacaat tcaaattaag gcaacaaaca  2700
tataccttcc atgaagcaca cacagacttt tgaaagcaag gacaatgact gcttgaattg   2760
aggccttgag gaatgaagct ttgaaggaaa agaatacttt gtttccagcc cccttcccac   2820
actcttcatg tgttaaccac tgccttcctg gaccttggag ccacggtgac tgtattacat   2880
gttgttatag aaaactgatt ttagagttct gatcgttcaa gagaatgatt aaatatacat   2940
ttcctaaaaa aaaaaaaaaa aaactcgagg gggggcccgg tacccaattc gccctatagt   3000
gagtcgtatt acaattcact ggccgtcgtt ttacaacgtc gtgactggga aaaccctggc   3060
gttacccaac ttaatcgcct tgcagcacat ccccctttcg ccagctggcg taatagcgaa   3120
gaggcccgca ccgatcgccc ttcccaacak ttgcgcagcc tgaatggcga atggcaaatt   3180
gtaagcgtta atattttgtt aaaattcgcg ttaaattttt gttaaatcag ctcatttttt   3240
aaccaatagg ccgaaatcgg caaaatccct tataaatcaa aagaatagac cgagataggg   3300
ttgagtgttg ttccagtttg gaacaagagt ccactattaa agtgttcacc gcggtga      3357
```

```
<210> 3
<211> 2406
<212> DNA
<213> Homo sapiens

<400> 3
ccacgcgtcc ggaatgaaca acttttcttc tcttgaatat atcttaacgc caaattttga     60
gtgctttttt gttacccatc ctcatatgtc ccagctggaa agaatcctgg gttggagcta    120
ctgcatgttg attgttttgt ttttcctttt ggctgttcat tttggtggct actataagga    180
aatctaacac aaacagcaac tgttttttgt tgtttacttt tgcatcttta cttgtggagc    240
tgtggcaagt cctcatatca aatacagaac atgatcttcc tcctgctaat gttgagcctg    300
gaattgcagc ttcaccagat agcagcttta ttcacagtga cagtccctaa ggaactgtac    360
ataatagagc atggcagcaa tgtgaccctg gaatgcaact ttgacactgg aagtcatgtg    420
aaccttggag caataacagc cagtttgcaa aaggtggaaa atgatacatc cccacaccgt    480
gaaagagcca ctttgctgga ggagcagctg cccctaggga aggcctcgtt ccacatacct    540
caagtccaag tgagggacga aggacagtac caatgcataa tcatctatgg ggtcgcctgg    600
```

```
gactacaagt acctgactct gaaagtcaaa gcttcctaca ggaaaataaa cactcacatc      660
ctaaaggttc cagaaacaga tgaggtagag ctcacctgcc aggctacagg ttatcctctg      720
gcagaagtat cctggccaaa cgtcagcgtt cctgccaaca ccagccactc caggacccct      780
gaaggcctct accaggtcac cagtgttctg cgcctaaagc cacccccctgg cagaaacttc     840
agctgtgtgt tctggaatac tcacgtgagg gaacttactt tggccagcat tgaccttcaa      900
agtcagatgg aacccaggac ccatccaact tggctgcttc acattttcat cccctcctgc      960
atcattgctt tcattttcat agccacagtg atagccctaa gaaaacaact ctgtcaaaag     1020
ctgtattctt caaaagacac aacaaaaaga cctgtcacca caacaaagag ggaagtgaac     1080
agtgctgtga atctgaacct gtggtcttgg gagccagggt gacctgatat gacatctaaa     1140
gaagcttctg gactctgaac aagaattcgg tggcctgcag agcttgccat ttgcactttt     1200
caaatgcctt tggatgaccc agcactttaa tctgaaacct gcaacaagac tagccaacac     1260
ctggccatga aacttgcccc ttcactgatc tggactcacc tctggagcct atggctttaa     1320
gcaagcacta ctgcacttta cagaattacc ccactggatc ctggacccac agaattcctt     1380
caggatcctt cttgctgcca gactgaaagc aaaaggaatt atttcccctc aagttttcta     1440
agtgatttcc aaaagcagag gtgtgtggaa atttccagta acagaaacag atgggttgcc     1500
aatagagtta ttttttatct atagcttcct ctgggtacta gaagaggcta ttgagactat     1560
gagctcacag acagggcttc gcacaaactc aaatcataat tgacatgttt tatggattac     1620
tggaatcttg atagcataat gaagttgttc taattaacag agagcattta aatatacact     1680
aagtgcacaa attgtggagt aaagtcatca agctctgttt ttgaggtcta agtcacaaag     1740
catttgtttt aacctgtaat ggcaccatgt ttaatggtgg tttttttttt gaactacatc     1800
tttcctttaa aaattattgg tttcttttta tttgttttta ccttagaaat caattatata     1860
cagtcaaaaa tatttgatat gctcatacgt tgtatctgca gcaatttcag ataagtagct     1920
aaaatggcca aagccccaaa ctaagcctcc ttttctggcc ctcaatatga ctttaaattt     1980
gacttttcag tgcctcagtt tgcacatctg taatacagca atgctaagta gtcaaggcct     2040
ttgataattg gcactatgga aatcctgcaa gatcccacta catatgtgtg gagcagaagg     2100
gtaactcggc tacagtaaca gcttaatttt gttaaatttg ttctttatac tggagccatg     2160
aagctcagag cattagctga cccttgaact attcaaatgg gcacattagc tagtataaca     2220
gacttacata ggtgggccta aagcaagctc cttaactgag caaaatttgg ggcttatgag     2280
aatgaaaggg tgtgaaattg actaacagac aaatcataca tctcagtttc tcaattctca     2340
tgtaaatcag agaatgcctt taaagaataa aactcaattg ttattcttca aaaaaaaaaa     2400
aaaaaa                                                                 2406


&lt;210&gt; 4
&lt;211&gt; 3059
&lt;212&gt; DNA
&lt;213&gt; Homo sapiens

&lt;400&gt; 4
ggcacgagct gtcatccgtt tccatgccgt gaggtccatt cacagaacac atccatggct        60
ctcatgctca gtttggttct gagtctcctc aagctgggat cagggcagtg gcaggtgttt       120
gggccagaca agcctgtcca ggccttggtg gggggaggacg cagcattctc ctgtttcctg      180
tctcctaaga ccaatgcaga ggccatggaa gtgcggttct tcaggggcca gttctctagc       240
gtggtccacc tctacaggga cgggaaggac cagccattta tgcagatgcc acagtatcaa       300
ggcaggacaa aactggtgaa ggattctatt gcggaggggc gcatctctct gaggctggaa       360
aacattactg tgttggatgc tggcctctat gggtgcagga ttagttccca gtcttactac       420
cagaaggcca tctgggagct acaggtgtca gcactgggct cagttcctct catttccatc       480
gcgggatatg ttgatagaga catccagcta ctctgtcagt cctcgggctg gttccccccgg      540
cccacagcga agtggaaagg tccacaagga caggatttgt ccacagactc caggacaaac       600
agagacatgc atggcctgtt tgatgtggag atctctctga ccgtccaaga gaacgccggg       660
agcatatcct gttccatgcg gcatgctcat ctgagccgag aggtggaatc cagggtacag       720
ataggagact ggagaagaaa gcacggacag gcaggtaaaa gaaaatattc ctcttcacac       780
atttatgact cctttccaag tctctcgttt atggattttt atatcctgag gcccgtgggt       840
ccctgcagag ccaagcttgt gatgggaact ctgaaattgc agattctggg ggaggtgcat       900
tttgtagaga agccccatag ccttcttcag atctctggag ggtccacaac actcaaaaag       960
ggtcccaatc cttggtcttt cccttctccc tgcgccctgt ttcccacgtg agcacggaac      1020
tgcctgctct ctctgcttgc tttcagaatt gagagacgcc cggaaacacg caggtaccaa      1080
cgcctgagag ggtaacagtg ggcatggagt aggaagatga ccagtgacag atatggagcc      1140
catccagctt gtagacagca aatctgtgat gcccgaatcc accccagggt gcagctgcct      1200
ctaaatacac ttcttggccc aggacttgga gggaaaagcg tagggactgg gtcagctagg      1260
aggggtcaca ggcaagacgc cagggaactg agggcattag tagctggctt ctaggggtct      1320
```

```
gtgcaaaggg gaacgaagtg aagttagcag gaactggtgg gtggaaggaa gctgaatcct      1380
ggagtcactc aaggtctcac aaagtcaaat agagggctta cgtgggaggg cagtggtagg      1440
gctgggtgaa catctcatgg ttgagcatct ccaagcatca gtgaggcacg gggctgccc       1500
tggagaaggt acatggctgg tgggatagtg ggactggccg gatcctaccc ggagccagtc      1560
tgcagtggga gggtcgacct cttgctccag cccagatttc gtcttcagta actcatgctt      1620
cctctctccc ccaccgcacc ccagtggagg tgactctgga tccagagacg gctcacccga      1680
agctctgcgt ttctgatctg aaaactgtaa cccatagaaa agctcctcag gaggtgcctc      1740
actctgagaa gagatttaca aggaagagtg tggtggcttc tcagggtttc caagcaggga      1800
aacattactg ggaggtggac gtgggacaaa atgtagggtg gtatgtggga gtgtgtcggg      1860
atgacgtaga cagggggaag aacaatgtga ctttgtctcc caacaatggg tattgggtcc      1920
tcagactgac aacagaacat ttgtatttca cattcaatcc ccattttatc agcctccccc      1980
ccagcacccc tcctacacga gtaggggtct tcctggacta tgagggtggg accatctcct      2040
tcttcaatac aaatgaccag tcccttattt ataccctgct gacatgtcag tttgaaggct      2100
tgttgagacc ctatatccag catgcgatgt atgacgagga aaaggggact cccatattca      2160
tatgtccagt gtcctgggga tgagacagag aagaccctgc ttaaagggcc ccacaccaca      2220
gacccagaca cagccaaggg agagtgctcc cgacaggtgg ccccagcttc ctctccggag      2280
cctgcgcaca gagagtcacg ccccccactc tcctttaggg agctgaggtt cttctgccct      2340
gagccctgca gcagcggcag tcacagcttc cagatgaggg gggattggcc tgaccctgtg      2400
ggagtcagaa gccatggctg ccctgaagtg gggacggaat agactcacat taggtttagt      2460
ttgtgaaaac tccatccagc taagcgatct tgaacaagtc acaacctccc aggctcctca      2520
tttgctagtc acggacagtg attcctgcct cacaggtgaa gattaaagag acaacgaatg      2580
tgaatcatgc ttgcaggttt gagggccaca gtgtttgcta atggatgtgt ttttatgatt      2640
atacattttc cccaccataa aactctgttt gccttaattc ccacattaat ttaacttttc      2700
ctcctatacc caaatccacc catggaatag ttaattggaa cacctgcctt tgtgaggctc      2760
caaagaataa agaggaggta ggatttttca ctgattctat aagcccagca ttacctgata      2820
ccaaaaccag gcaaagaaaa cagaagaaga ggaaggaaaa ctacaggtcc atatccctca      2880
ttaacacaga cacaaaaatt ctaaataaaa ttttaacaaa ttaaactaaa caatatattt      2940
aaagatgata tataactact cagtgtggtt tgtcccacaa atgcagagtt ggtttaatat      3000
ttaaatatca accagtgtaa ttcagcacat taataaagta aaaaaaaaaa aaaaaaaaa       3059


&lt;210&gt; 5
&lt;211&gt; 2682
&lt;212&gt; DNA
&lt;213&gt; Homo sapiens

&lt;220&gt;
&lt;221&gt; SITE
&lt;222&gt; (1)
&lt;223&gt; n equals a,t,g, or c

&lt;220&gt;
&lt;221&gt; SITE
&lt;222&gt; (2)
&lt;223&gt; n equals a,t,g, or c

&lt;400&gt; 5
nncacgagcc tgtgcccctg gaaaggttgg agacttgggg gacgactgga gaattgccat        60
ttgaggacca aaggagaaaa gaaactacac gctaattcta gaaggcctcc tgtccctgcc       120
tgctctgggt gctcatggaa ccagctgctg ccctgcactt ctcccggcca gcctccctcc       180
tcctcctcct cagcctgtgt gcactggtct cagcccagtt tactgtcgtg ggccagcta       240
atcccatcct ggccatggtg ggagaaaaca ctacattacg ctgccatctg tcacccgaga       300
aaaatgctga ggacatggag gtgcggtggt tccggtctca gttctccccc gcagtgtttg       360
tgtataaggg tgggagagag agaacagagg agcagatgga ggagtaccgg ggaagaatca       420
cctttgtgag caaagacatc aacaggggca gcgtggccct ggtcatacat aacgtcacag       480
cccaggagaa tgggatctac cgctgttact tccaagaagg caggtcctac gatgaggcca       540
tcctacgcct cgtggtggca ggccttgggt ctaagcccct cattgaaatc aaggcccaag       600
aggatgggag catctggctg gagtgcatat ctggagggtg gtacccagag cccctcacag       660
tgtggaggga cccctacggt gaggttgtgc ccgccctgaa ggaggtttcc atcgctgatg       720
ctgacggcct cttcatggtc accacagctg tgatcatcag agacaagtat gtgaggaatg       780
tgtcctgctc tgtcaacaac accctgctcg gccaggagaa ggaaactgtc atttttattc       840
```

```
cagaatcctt tatgcccagc gcatctccct ggatggtggc cctagctgtc atcctgaccg    900
catctccctg gatggtgtcc atgactgtca tcctggctgt tttcatcatc ttcatggctg    960
tcagcatctg ttgcatcaag aaacttcaaa gggaaaaaaa gattctgtca ggggaaaaga   1020
aagttgaaca agaggaaaaa gaaattgcac agcaacttca agaagaattg cgatggagaa   1080
gaacattctt acatgctgct gatgtggtcc tggatccaga caccgctcat cccgagctct   1140
tcctgtcaga ggaccggaga agtgtgaggc ggggcccta caggcagaga gtgcctgaca    1200
acccagagag attcgacagt cagccttgtg tcctgggatg ggagagcttc gcctcaggga   1260
aacattacag gggaaacttc acagagtggg gacccaccag agcctataga atcaattcct   1320
tggactcaca gccatgcaga aagccctggc catctcagca gccaccgcac aacccccta    1380
atgaaagaca cgccctcctc ccctctggtc acgtaagaga acatcttcca gctgcctttt   1440
tcacacccac tccagccctc tgccccagtt ttctcctcct cactagtctg tggctttagt   1500
agttcctttg cttgtaatta tgggatggga tccaggcata gggaactagt tgtttcatag   1560
ctcccagtca aaaagaaagt gagagaagct gttgggcagc gaacctactg tttaaaatca   1620
ggataaccac attaagccca atatgccagt tggcaccaga tgctgtggac ttggaatgag   1680
gccaacaggg ttcaccagga tgagagagga gagaggaatc cacaggacca ccagaaggga   1740
gagggaacca gatatgcaga tcagagatag aggaagtgtt gagaggaaag gggaggtcct   1800
gctgattcct cagaatggct tctggaccct ggagatgttt ggaaaccaat accgggccct   1860
gtcctcccct gagaggattc tccctttgaa ggagtccctt tgccgggtgg gcgtcttcct   1920
ggactatgaa gctggagatg tctccttcta caacatgagg gacagatcac acatctacac   1980
atgtccccgt tcagccttta atgtgcctgt gaggccattc ttcaggttag ggtctgatga   2040
cagccccatc ttcatctgcc ctgcactcac aggagccagt ggggtcatgg tgcctgaaga   2100
gggcctgaaa cttcacagag tggggaccca ccaaggttgt aaggatggct aagtcccacc   2160
ataagagcta aagggtcctg ggagatgatg gctcatttcc acccaacccc aggatttcca   2220
cagcacacac ccacaggcct ggacctggga tgaagatgaa tgaagaacat ggactcatgt   2280
ggatgtggtt tggctcagat gtccctgcaa taaacaaggg gtcagtactt agtccctgag   2340
tgtggttgag gtttgaggtc ctggtcgagc agggcagtac tggaccaggt ctacgtcagc   2400
attcaggttc aatggggaca ccagtggctt caaacttcct gatctaatta tgtttttaga   2460
cacttagaag ttattgagga ctttaaagaa cttttgttta tttgggttaa tatttatgac   2520
atttgaccat tgaaacaaaa atttaaaatg ttatctttta atttatgtta aaatagcatt   2580
aataaatcag ttataggtta atgtagatag gatgttttgt gaaaaagcaa tctattgtgt   2640
ccaaataaaa aaacaaaaag tgtaaaaaaa aaaaaaaaaa aa                      2682
```

```
<210> 6
<211> 1726
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (1)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (2)
<223> n equals a,t,g, or c

<400> 6
nncgattcgg ctccaaactc cggcgctgca gccgatcgga ctctgggccg cggtgggcac     60
cgcgcgcagc tagggagccg agaaccgcgg cgagccccga ggacgcccag agcgcgaggg    120
tcgctgcgcc tcgcagagcc ggagccgagt cgagccgggc gcccgggctg cctggagacg    180
ccgtgacttt gaagtgtaac ttcaagacag atgggcgcat gcgggagatc gtgtggtacc    240
gggtgacgga tggtggcacc atcaagcaaa agatcttcac cttcgacgcc atgttctcca    300
ccaactactc acacatggag aactaccgca agcgagagga cctggtgtac cagtccactg    360
tgaggctgcc cgaggtccgg atctcagaca atggtcccta tgagtgccat gtgggcatct    420
acgaccgcgc caccagggag aaggtggtcc tggcatcagg caacatcttc ctcaacgtca    480
tggctcctcc cacctccatt gaagtggtgg ctgctgacac accagccccc ttcagccgct    540
accaagccca gaacttcacg ctggtctgca tcgtgtctgg aggaaaacca gcacccatgg    600
tttatttcaa acgagatggg gaaccaatcg acgcagtgcc cctatcagag ccaccagctg    660
cgagctccgg ccccctacag gacagcaggc ccttccgcag ccttctgcac cgtgacctgg    720
```

```
atgacaccaa gatgcagaag tcactgtccc tcctggacgc cgagaaccgg ggtgggcgac      780
cctacacgga gcgcccctcc cgtggcctga ccccagatcc caacatcctc ctccagccaa      840
ccacagagaa cataccagag acggtcgtga gccgtgagtt tccccgctgg gtccacagcg      900
ccgagcccac ctacttcctg cgccacagcc gcaccccgag cagtgacggc actgtggaag      960
tacgtgccct gctcacctgg accctcaacc cacagatcga caacgaggcc ctcttcagct     1020
gcgaggtcaa gcacccagct ctgtcgatgc ccatgcaggc agaggtcacg ctggttgccc     1080
ccaaaggacc caaaattgtg atgacgccca gcagagcccg ggtaggggac acagtgagga     1140
ttctggtcca tgggtttcag aacgaagtct tcccggagcc catgttcacg tggacgcggg     1200
ttgggagccg cctcctggac ggcagcgctg agttcgacgg gaaggagctg gtgctggagc     1260
gggttcccgc cgagctcaat ggctccatgt atcgctgcac cgcccagaac ccactgggct     1320
ccaccgacac gcacacccgg ctcatcgtgt ttgaaaaccc aaatatccca agaggaacgg     1380
aggactctaa tggttccatt ggccccactg gtgcccggct caccttggtg ctcgccctga     1440
cagtgattct ggagctgacg tgaaggcacc cgccccggcc actccatcag gcactgacat     1500
ctccgcgacc ggttttcatt tcttttctaa actatttcca gtcttgttct tagtctcttt     1560
ccatctgtgt cttggcttct tcagtcggtt taattaaaac aaacagaaca attttcccca     1620
caaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa     1680
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaa                    1726


<210> 7
<211> 1021
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (1)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (2)
<223> n equals a,t,g, or c

<400> 7
nncacgagcc tgtgcccctg gaaaggttgg agacttgggg gacgactgga gaattgccat       60
ttgaggacca aaggagaaaa gaaactacac gctaattcta gaaggcctcc tgtccctgcc      120
tgctctgggt gctcatggaa ccagctgctg ccctgcactt ctcccggcca gcctccctcc      180
tcctcctcct cagcctgtgt gcactggtct cagcccaggt cactgtcgtg gggcccactg      240
atcccatcct ggccatggtg ggagaaaaca ctacgttacg atgctgtctg tcacccgagg      300
aaaatgctga ggacatggag gtgcggtggt tccagtctca gttctcccct gcagtgtttg      360
tgtataaggg tggaagagag agaacagagg agcagaagga ggagtaccga gggagaacca      420
cctttgtgag caaagacagc aggggcagcg tggccctgat catacacaat gtcacagccg      480
aggataacgg catctaccag tgttacttcc aagaaggcag gtcctgcaat gaggccatcc      540
tgcaccttgt ggtggcagac cagcacaatc ctctttcctg gatccccatt ccgcagggga      600
cactctccct atgaaaagaa gattccaggg gaaaaatcct tcctcctgca caagggccac      660
catgagtgag tttgccctgc taagccgtgg gcttgacttc ttgagaagca catgcagaac      720
tcagttgagg ccatgagccg gggaaaaatg gtgaatctcg gaagagaagt cctatgcctg      780
ccttagcact gagctgtgca cttctgagag tgagaggaga caccatcaat aattgtcttg      840
ggacaactgg aataaacagt gactgcccag agaactacga tatttgaaat cttatttctt      900
gatgaatatt catcctgact tctttcctga aatgctgttt gcaaagagag tgacttatat      960
gtaagtagag cgttttatta aagcaagact taatacagaa gcaaaaaaaa aaaaaaaaaa     1020
a                                                                     1021


<210> 8
<211> 1835
<212> DNA
<213> Homo sapiens

<220>
```

<221> SITE
<222> (1)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (2)
<223> n equals a,t,g, or c

<400> 8
nnacatccat ggctctaatg ctcagtttgg ttctgagtct cctcaagctg ggatcagggc 60
agtggcaggt gtttgggcca gacaagcctg tccaggcctt ggtgggggag gacgcagcat 120
tctcctgttt cctgtctcct aagaccaatg cagaggccat ggaagtgcgg ttcttcaggg 180
gccagttctc tagcgtggtc cacctctaca gggacgggaa ggaccagcca tttatgcaga 240
tgccacagta tcaaggcagg acaaaactgg tgaaggattc tattgcggag ggcgcatct 300
ctctgaggct ggaaaacatt actgtgttgg atgctggcct ctatgggtgc aggattagtt 360
cccagtctta ctaccagaag gccatctggg agctacaggt gtcagcactg ggctcagttc 420
ctctcatttc catcacggga tatgttgata gagacatcca gctactctgt cagtcctcgg 480
gctggttccc ccggcccaca gcgaagtgga aaggtccaca aggacaggat ttgtccacag 540
actccaggac aaacagagac atgcatggcc tgtttgatgt ggagatctct ctgaccgtcc 600
aagagaacgc cgggagcata tcctgttcca tgcggcatgc tcatctgagc cgagaggtgg 660
aatccagggt acagatagga gataccttttt tcgagcctat atcgtggcac ctggctacca 720
aagtactggg aatactctgc tgtggcctat tttttggcat tgttggactg aagattttct 780
tctccaaatt ccagtggaaa atccaggcgg aactggactg gagaagaaag cacggacagg 840
cagaattgag agacgcccgg aaacacgcag tggaggtgac tctggatcca gagacggctc 900
acccgaagct ctgcgtttct gatctgaaaa ctgtaaccca tagaaaagct ccccaggagg 960
tgcctcactc tgagaagaga tttacaagga agagtgtggt ggcttctcag agtttccaag 1020
cagggaaaca ttactgggag gtggacggag gacacaataa aaggtggcgc gtgggagtgt 1080
gccgggatga tgtggacagg aggaaggagt acgtgacttt gtctcccgat catgggtact 1140
gggtcctcag actgaatgga gaacatttgt atttcacatt aaatccccgt tttatcagcg 1200
tcttccccag gaccccacct acaaaaatag ggtcttcct ggactatgag tgtgggacca 1260
tctccttctt caacataaat gaccagtccc ttatttatac cctgacatgt cggtttgaag 1320
gcttattgag gccctacatt gagtatccgt cctataatga gcaaaatgga actcccagag 1380
acaagcaaca gtgagtcctc ctcacaggca accacgccct tcctccccag gggtgaaatg 1440
taggatgaat cacatcccac attcttcttt agggatatta aggtctctct cccagatcca 1500
aagtcccgca gcagccggcc aaggtggctt ccagatgaag gggactggc ctgtccacat 1560
gggagtcagg tgtcatggct gccctgagct gggagggaag aaggctgaca ttacatttag 1620
tttgctctca ctccatctgg ctaagtgatc ttgaaatacc acctctcagg tgaagaaccg 1680
tcaggaattc ccatctcaca ggctgtggtg tagattaagt agacaaggaa tgtgaataat 1740
gcttagatct tattgatgac agagtgtatc ctaatggttt gttcattata ttacactttc 1800
agtaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaa 1835

<210> 9
<211> 2626
<212> DNA
<213> Homo sapiens

<400> 9
aattcggcac gagaggcagc ggcagctcca ctcagccagt acccaggata cgctggggaa 60
ccttccccca gccatggctt ccctggggca gatcctcttc tggagcataa tttagcatca 120
tcattattct ggctgaagca attgcactca tcattggctt tggtatttca gggagacact 180
ccatcacagt cactactgtc gcctcagctg ggaacattgg ggaggatgga atcctgagct 240
gcacttttga acctgacatc aaactttctg atatcgtgat acaatggctg aaggaaggtg 300
ttttaggctt ggtccatgag ttcaaagaag gccaaagatg agctgtcgga gcaggatgaa 360
atgttcagag gccgggacag cagtgtttgc tgatcaagtg atagttggca atgcctcttt 420
tgcggctgaa aaacgtgcaa ctcacagatg ctggcaccta caaatgttat atcatcactt 480
ctaaaggcaa ggggaatgct aaccttgagt ataaaactgg agccttcagc atgccggaag 540
tgaatgtgga ctataatgcc agctcagaga ccttgcggtg tgaggctccc cgatggttcc 600
cccagcccac agtggtctgg gcatcccaag ttgaccaggg agccaacttc tcggaagtct 660
ccaataccag ctttgagctg aactctgaga atgtgaccat gaaggttgtg tctgtgctct 720

```
acaatgttac gatcaacaac acatactcct gtatgattga aaatgacatt gccaaagcaa      780
caggggatat caaagtgaca gaatcggaga tcaaaaggcg gagtcaccta cagctgctaa      840
actcaaaggc ttctctgtgt gtctcttctt tctttgccat cagctgggca cttctgcctc      900
tcagccctta cctgatgcta aaataatgtg ccttggccac aaaaaagcat gcaaagtcat      960
tgttacaaca gggatctaca gaactatttc accaccagat atgacctagt tttatatttc     1020
tgggaggaaa tgaattcata tctagaagtc tggagtgagc aaacaagagc aagaaacaaa     1080
aagaagccaa aagcagaagg ctccaatatg aacaagataa atctatcttc aaagacatat     1140
tagaagttgg gaaaataatt catgtgaact agacaagtgt gttaagagtg ataagtaaaa     1200
tgcacgtgga gacaagtgca tccccagatc tcagggacct ccccctgcct gtcacctggg     1260
gatgagagga caggatagtg catgttcttt gtctctgaat ttttagttat atgtgctgta     1320
atgttgctct gaggaagccc ctggaaagtc tatcccaaca tatccacatc ttatattcca     1380
caaattaagc tgtagtatgt accctaagac gctgctaatc gactgccact tcgcaactca     1440
ggggcggctg cattttagta atgggtcaaa tgattcactt tttatgatgc ttccaaaggt     1500
gccttggctt ctcttcccaa ctgacaaatg ccaaaagttg agaaaaatga tcataatttt     1560
agcataaaca gagcaagtcg gcgacaccga ttttataaat aaactgagca ccttcttttt     1620
aaacaaacaa atgcgggttt atttctcaga tgatgttcat cccgtgaatg gtccagggaa     1680
ggacctttca ccttgactat atggcattat gtcatcacaa gctctgaggc ttctcctttc     1740
catcctgcgt ggacagctaa gacctcagtt ttcaatagca tctagagcag tgggactcag     1800
ctggggtgat ttcgcccccc atctccgggg gaatgtctga agacaatttt ggttacctca     1860
atgagggagt ggaggaggat acagtgctac taccaactag tggataaagg ccagggatgc     1920
tgctcaaccc tcctaccatg tacaggacgt ctccccatta caactaccca atccgaagtg     1980
tcaaactgtg tcaggactaa gaacccctgg ttttgagtag aaaagggcct ggaaagaggg     2040
gagccaacaa atctgtctgc ttcctcacat tagtcattgg caaataagca ttctgtctct     2100
ttggctgctg cctcagcaca gagagccaga actctatcgg gcaccaggat aacatctctc     2160
agtgaacaga gttgacaagg cctatgggaa atgcctgatg ggattatctt cagcttgttg     2220
agcttctaag tttctttccc ttcattctac cctgcaagcc aagttctgta agagaaatgc     2280
ctgagttcta gctcaggttt tcttactctg aatttagatc tccagaccct tcctggccac     2340
aattcaaatt aaggcaacaa acatatacct tccatgaagc acacacagac ttttgaaagc     2400
aaggacaatg actgcttgaa ttgaggcctt gaggaatgaa gctttgaagg aaaagaatac     2460
tttgtttcca gcccccttcc cacactcttc atgtgttaac cactgccttc ctggaccttg     2520
gagccacggt gactgtatta catgttgtta tagaaaactg attttagagt tctgatcgtt     2580
caagagaatg attaaatata catttcctaa aaaaaaaaaa aaaaaa                    2626
```

<210> 10
<211> 1675
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (1549)
<223> n equals a,t,g, or c

<400> 10

```
gtacgacyca ctatagggwg agagctatga cgtcgcatgc acgcgtaasc ttgggcccct       60
cgagggatcc tctagagcgg ccgccctttt tttttttttt tttgaagaat aacaattgag      120
ttttattctt taaaggcatt ctctgattta catgagaatt gagaaactga gatgtatgat      180
ttgtctgtta gtcaatttca caccctttca ttctcataag ccccaaattt tgctcagtta      240
aggagcttgc tttaggccca cctatgtaag tctgttatac tagctaatgt gcccatttga      300
atagttcaag ggtcagctaa tgctctgagc ttcatggctc cagtataaag aacaaattta      360
acaaaattaa gctgttactg tagccgagtt acccttctgc tccacacata tgtagtggga      420
tcttgcagga tttccatagt gccaattatc aaaggccttg actacttagc attgctgtat      480
tacagatgtg caaactgagg cactgaaaag tcaaatttaa agtcatattg agggccagaa      540
aaggaggctt agtttggggc tttggccatt ttagctactt atctgaaatt gctgcagata      600
caacgtatga gcatatcaaa tatttttgac tgtatataat tgatttctaa ggtaaaaaca      660
aataaaaaga aaccaataat ttttaaagga aagatgtagt tcaaaaaaaa aaccaccatt      720
aaacatggtg ccattacagg ttaaaacaaa tgctttgtga cttagacctc aaaaacagag      780
cttgatgact ttactccaca atttgtgcac ttagtgtata tttaaatgct ctctgttaat      840
tagaacaact tcattatgct atcaagattc cagtaatcca taaaacatgt caattatgat      900
ttgagtttgt gcgaagccct gtctgtgagc tcatagtctc aatagcctct tctagtaccc      960
```

```
agaggaagct atagataaaa aataactcta ttggcaaccc atctgtttct gttactggaa    1020
atttccacac acctctgctt ttggaaatca cttagaaaac ttgaggggaa ataattcctt    1080
ttgctttcag tctggcagca agaaggatcc tgaaggaatt ctgtgggtcc aggatccagt    1140
ggggtaattc tgtaaagtgc agtagtgctt gcttaaagcc ataggctcca gaggtgagtc    1200
cagatcagtg aaggggcaag tttcatggcc aggtgttggc tagtcttgtt gcaggtttca    1260
gattaaagtg ctgggtcatc caaaggcatt tgaaaagtgc aaatggcaag ctctgcaggc    1320
caccgaattc ttgttcagag tccagaagct tctttagatg tcatatcagg tcaccctggc    1380
tcccaagacc acaggttcag atagcactgt tcacttccct ctttgttgtg gtgacaggtc    1440
tttttgttgt gtcttttgaa gaatacagct tttgacagag ttgttttctt agggctrtca    1500
ckgkggctat gaaaatgaaa gcaatgatgc aggaggggat gaaaatgtna agcagccaag    1560
ttggatgggt cctgggttcc atctgacttt gaaggtcaat gctggccaaa gtaagttccc    1620
tcacgtgagt attccagaac acacagctga agtttctgcc agggggtggc tttag         1675
```

<210> 11
<211> 786
<212> DNA
<213> Homo sapiens

<220>
<221> SITE
<222> (754)
<223> n equals a,t,g, or c

<220>
<221> SITE
<222> (778)
<223> n equals a,t,g, or c

<400> 11

```
ggaatgaaca actttcttc tcttgaatat atcttaacgc caaattttga gtgctttttt     60
gttacccatc ctcatatgtc ccagctggaa agaatcctgg gttggagcta ctgcatgttg    120
attgttttgt ttttcctttt ggctgttcat tttggtggct actataagga aatctaacac    180
aaacagcaac tgttttttgt tgtttacttt tgcatcttta cttgtggagc tgtggcaagt    240
cctcatatca aatacagaac atgatcttcc tcctgctaat gttgagcctg gaattgcagc    300
ttcaccagat agcagcttta ttcacagtga cagtccctaa ggaactgtac ataatagagc    360
atggcagcaa tgtgaccctg gaatgcaact ttgacactgg aagtcatgtg aaccttggag    420
caataacagc cagtttgcaa aaggtggaaa atgatacatc cccacaccgt gaaagagcca    480
ctttgctgga ggagcagctg cccctaggga aggcctcgtt cccatmcctc aagtycaagt    540
gagggacgaa ggacagtacc aatgcataat catctatggg gtcgcctggg actacaagta    600
cctgactctg aaagtcaaag cttcctacag gaaaataaac actcacatcc taaaggttcc    660
agaaacagat gaggtagagc tcacctgcca ggctacaggt tatcctctgg cagaagtatc    720
ctggccaaac gtcagcgttc ctgccaacac cagncactcc aggacccctg aaggcctnta    780
ccaggt                                                               786
```

<210> 12
<211> 2008
<212> DNA
<213> Homo sapiens

<400> 12

```
cgggggcttt ctaacgggaa aaactctact aaagggttca aaagctggag ctccaccgcg     60
gtggcggccg ctctagaact agtggatccc ccgggctgca ggaattcggc acgagctcgt    120
gccgaattcg gcacgagtca cagaacacat ccatggctct matgctcagt ttggttctga    180
gtctcctcaa gctgggwtca gggcagtggc aggtgtttgg gccagacaag cctgtccagg    240
ccttggtggg ggaggacgca gcattctcct gtttcctgtc tcctaagacc aatgcagagg    300
ccatggaagt gcggttcttc aggggccagt tctctagcgt ggtccacctc tacagggacg    360
ggaaggacca gccatttatg cagatgccac agtatcaagg caggacaaaa ctggtgaagg    420
attctattgc ggagggggcgc atctctctga ggctggaaaa cattactgtg ttggatgctg    480
gcctctatgg gtgcaggatt agttcccagt cttactacca gaaggccatc tgggagctac    540
```

```
aggtgtcagc actgggctca gttcctctca tttccatcac gggatatgtt gatagagaca     600
tccagctact ctgtcagtcc tcgggctggt tcccccggcc cacagcgaag tggaaaggtc     660
cacaaggaca ggatttgtcc acagactcca ggacaaacag agacatgcat ggcctgtttg     720
atgtggagat ctctctgacc gtccaagaga acgccgggag catatcctgt tccatgcggc     780
atgctcatct gagccgagag gtggaatcca gggtacagat aggagatacc tttttcgagc     840
ctatatcgtg gmacctggyt accaaagtac tgggaatact ctgctgtggc ctatttttg      900
gcattgttgg actgaagatt ttcttctcca aattccagtg gaaaatccag gcggaactgg     960
actggagaag aaagcacgga caggcagaat tgagagacgc ccggaaacac gcagtggagg    1020
tgactctgga tccagagacg gctcacccga agctctgcgt ttctgatctg aaaactgtaa    1080
cccatagaaa agctccccag gaggtgcctc actctgagaa gagatttaca aggaagagtg    1140
tggtggcttc tcagagtttc caagcaggga aacattactg ggaggtggac ggaggacaca    1200
ataaaaggtg gcgcgtggga gtgtgccggg atgatgtgga caggaggaag gagtacgtga    1260
ctttgtctcc cgatcatggg tactgggtcc tcagactgaa tggagaacat ttgtatttca    1320
cattaaatcc ccgttttatc agcgtcttcc ccaggacccc acctacaaaa ataggggtct    1380
tcctggacta tgagtgtggg accatctcct tcttcaacat aaatgaccag tcccttattt    1440
ataccctgac atgtcggttt gaaggcttat tgaggcccta cattgagtat ccgtcctata    1500
atgagcaaaa tggaactccc agagacaagc aacagtgagt cctcctcaca ggcaaccacg    1560
cccttcctcc ccaggggtga aatgtaggat gaatcacatc ccacattctt ctttagggat    1620
attaaggtct ctctcccaga tccaaagtcc cgcagcagcc ggccaaggtg gcttccagat    1680
gaagggggac tggcctgtcc acatgggagt caggtgtcat ggctgccctg agctgggagg    1740
gaagaaggct gacattacat ttagtttgct ctcactccat ctggctaagt gatcttgaaa    1800
taccacctct caggtgaaga accgtcagga attcccatct cacaggctgt ggtgtagatt    1860
aagtagacaa ggaatgtgaa taatgcttag atcttattga tgacagagtg tatcctaatg    1920
gtttgttcat tatattacac tttcagtaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaamc    1980
tcgagggggg gcccggtacc caattcgg                                       2008
```

```
<210> 13
<211> 2799
<212> DNA
<213> Homo sapiens

<400> 13
tgggacactg tggaagccca gagaatctga tcccgggtcc cacaacttca catatcgcga      60
gtaagtggga ggcaaagaaa attctttttc tcctcttttg ggacagtttg tgactagtaa     120
tgcctgtgcc cctggaaagg ttggagactt gggggacgac tggagaattg ccatttgagg     180
accaaaggag aaaagaaact acacgctaat tctagaaggc ctcctgtccc tgcctgctct     240
gggtgctcat ggaaccagct gctgccctgc acttctcccg gccagcctcc ctcctcctcc     300
tcctcagcct gtgtgcactg gtctcagccc agtttactgt cgtggggcca gctaatccca     360
tcctggccat ggtgggagaa aacactacat tacgctgcca tctgtcaccc gagaaaaatg     420
ctgaggacat ggaggtgcgg tggttccggt ctcagttctc cccgcagtg tttgtgtata      480
agggtgggag agagagaaca gaggagcaga tggaggagta ccggggaaga atcacctttg     540
tgagcaaaga catcaacagg ggcagcgtgg ccctggtcat acataacgtc acagcccagg     600
agaatgggat ctaccgctgt tacttccaag aaggcaggtc ctacgatgag gccatcctac     660
gcctcgtggt ggcaggcctt gggtctaagc ccctcattga aatcaaggcc caagaggatg     720
ggagcatctg gctggagtgc atatctggag ggtggtaccc agagcccctc acagtgtgga     780
gggaccccta cggtgaggtt gtgcccgccc tgaaggaggt ttccatcgct gatgctgacg     840
gcctcttcat ggtcaccaca gctgtgatca tcagagacaa gtatgtgagg aatgtgtcct     900
gctctgtcaa caacaccctg ctcggccagg agaaggaaac tgtcattttt attccagaat     960
cctttatgcc cagcgcatct ccctggatgg tggccctagc tgtcatcctg accgcatctc    1020
cctggatggt gtccatgact gtcatcctgg ctgttttcat catcttcatg gctgtcagca    1080
tctgttgcat caagaaactt caaagggaaa aaaagattct gtcaggggaa aagaaagttg    1140
aacaagagga aaaagaaatt gcacagcaac ttcaagaaga attgcgatgg agaagaacat    1200
tcttacatgc tgctgatgtg gtcctggatc cagacaccgc tcatcccgag ctcttcctgt    1260
cagaggaccg gagaagtgtg aggcggggcc cctacaggca gagagtgcct gacaacccag    1320
agagattcga cagtcagcct tgtgtcctgg gatgggagag cttcgcctca gggaaacatt    1380
acaggggaaa cttcacagag tggggaccca ccagagccta tagaatcaat tccttggact    1440
cacagccatg cagataagcc ctggccatct cagcagccac cgcacaaccc ccctaatgaa    1500
agacacgccc tcctcccctc tggtcacgta agagaacatc ttccagctgc ctttttcaca    1560
cccactccag ccctctgccc cagttttctc ctcctcacta gtctgtggct ttagtagttc    1620
ctttgcttgt aattatggga tgggatccag gcatagggaa ctagttgttt catagctccc    1680
```

```
agtcaaaaag aaagtgagag aagctgttgg gcagcgaacc tactgtttaa aatcaggata     1740
accacattaa gcccaatatg ccagttggca ccagatgctg tggacttgga atgaggccaa     1800
cagggttcac caggatgaga gaggagagag gaatccacag gaccaccaga agggagaggg     1860
aaccagatat gcagatcaga gatagaggaa gtgttgagag gaaaggggag gtcctgctga     1920
ttcctcagaa tggcttctgg accctggaga tgtttggaaa ccaataccgg gccctgtcct     1980
cccctgagag gattctccct ttgaaggagt ccctttgccg ggtgggcgtc ttcctggact     2040
atgaagctgg agatgtctcc ttctacaaca tgagggacag atcacacatc tacacatgtc     2100
cccgttcagc ctttactgtg cctgtgaggc ccttcttcag gttagggtct gatgacagcc     2160
ccatcttcat ctgccctgca ctcacaggag ccagtggggt catggtgcct gaagagggcc     2220
tgaaacttca cagagtgggg acccaccaag gttgtaaggg atggctaagt cccaccataa     2280
gagctaaagg gtcctgggag atgatggctc atttccaccc aaccccagga tttccacagc     2340
acacacccac aggcctggac ctgggatgaa gatgaatgaa gaacatggac tcatgtggat     2400
gtggtttggc tcagatgtcc ctgcaataaa caaggggtca gtacttagtc cctgagtgtg     2460
gttgaggttt gaggtcctgg tcgagcaggg cagtactgga ccaggtctac gtcagcattc     2520
aggttcaatg gggacacca gtggcttcaa acttcctgat ctaattatgt ttttagacac     2580
ttagaagtta ttgaggactt taaagaactt ttgtttattt gggttaatat ttatgacatt     2640
tgaccattga aacaaaaatt taaaatgtta tcttttaatt tatgttaaaa tagcattaat     2700
aaatcagtta taggttaatg tagataggat gttttgtgaa aaagcaatct attgtgtcca     2760
aataaaaaaa caaaaagtgt aaaaaaaaaa aaaaaaaaa                            2799
```

<210> 14
<211> 282
<212> PRT
<213> Homo sapiens

<400> 14

```
Met Ala Ser Leu Gly Gln Ile Leu Phe Trp Ser Ile Ile Ser Ile Ile
1               5                   10                  15

Ile Ile Leu Ala Gly Ala Ile Ala Leu Ile Ile Gly Phe Gly Ile Ser
            20                  25                  30

Gly Arg His Ser Ile Thr Val Thr Thr Val Ala Ser Ala Gly Asn Ile
        35                  40                  45

Gly Glu Asp Gly Ile Leu Ser Cys Thr Phe Glu Pro Asp Ile Lys Leu
    50                  55                  60

Ser Asp Ile Val Ile Gln Trp Leu Lys Glu Gly Val Leu Gly Leu Val
65                  70                  75                  80

His Glu Phe Lys Glu Gly Lys Asp Glu Leu Ser Glu Gln Asp Glu Met
                85                  90                  95

Phe Arg Gly Arg Thr Ala Val Phe Ala Asp Gln Val Ile Val Gly Asn
            100                 105                 110

Ala Ser Leu Arg Leu Lys Asn Val Gln Leu Thr Asp Ala Gly Thr Tyr
        115                 120                 125

Lys Cys Tyr Ile Ile Thr Ser Lys Gly Lys Gly Asn Ala Asn Leu Glu
    130                 135                 140

Tyr Lys Thr Gly Ala Phe Ser Met Pro Glu Val Asn Val Asp Tyr Asn
145                 150                 155                 160

Ala Ser Ser Glu Thr Leu Arg Cys Glu Ala Pro Arg Trp Phe Pro Gln
                165                 170                 175

Pro Thr Val Val Trp Ala Ser Gln Val Asp Gln Gly Ala Asn Phe Ser
```

180 185 190

Glu Val Ser Asn Thr Ser Phe Glu Leu Asn Ser Glu Asn Val Thr Met
195 200 205

Lys Val Val Ser Val Leu Tyr Asn Val Thr Ile Asn Asn Thr Tyr Ser
210 215 220

Cys Met Ile Glu Asn Asp Ile Ala Lys Ala Thr Gly Asp Ile Lys Val
225 230 235 240

Thr Glu Ser Glu Ile Lys Arg Arg Ser His Leu Gln Leu Leu Asn Ser
245 250 255

Lys Ala Ser Leu Cys Val Ser Ser Phe Phe Ala Ile Ser Trp Ala Leu
260 265 270

Leu Pro Leu Ser Pro Tyr Leu Met Leu Lys
275 280

<210> 15
<211> 283
<212> PRT
<213> Homo sapiens

<400> 15
Met Ile Phe Leu Leu Leu Met Leu Ser Leu Glu Leu Gln Leu His Gln
1 5 10 15

Ile Ala Ala Leu Phe Thr Val Thr Val Pro Lys Glu Leu Tyr Ile Ile
20 25 30

Glu His Gly Ser Asn Val Thr Leu Glu Cys Asn Phe Asp Thr Gly Ser
35 40 45

His Val Asn Leu Gly Ala Ile Thr Ala Ser Leu Gln Lys Val Glu Asn
50 55 60

Asp Thr Ser Pro His Arg Glu Arg Ala Thr Leu Leu Glu Glu Gln Leu
65 70 75 80

Pro Leu Gly Lys Ala Ser Phe His Ile Pro Gln Val Gln Val Arg Asp
85 90 95

Glu Gly Gln Tyr Gln Cys Ile Ile Ile Tyr Gly Val Ala Trp Asp Tyr
100 105 110

Lys Tyr Leu Thr Leu Lys Val Lys Ala Ser Tyr Arg Lys Ile Asn Thr
115 120 125

His Ile Leu Lys Val Pro Glu Thr Asp Glu Val Glu Leu Thr Cys Gln
130 135 140

Ala Thr Gly Tyr Pro Leu Ala Glu Val Ser Trp Pro Asn Val Ser Val
145 150 155 160

Pro Ala Asn Thr Ser His Ser Arg Thr Pro Glu Gly Leu Tyr Gln Val
165 170 175

Thr Ser Val Leu Arg Leu Lys Pro Pro Pro Gly Arg Asn Phe Ser Cys

```
            180                 185                 190

Val Phe Trp Asn Thr His Val Arg Glu Leu Thr Leu Ala Ser Ile Asp
        195                 200                 205

Leu Gln Ser Gln Met Glu Pro Arg Thr His Pro Thr Trp Leu Leu His
    210                 215                 220

Ile Phe Ile Pro Ser Cys Ile Ile Ala Phe Ile Phe Ile Ala Thr Val
225                 230                 235                 240

Ile Ala Leu Arg Lys Gln Leu Cys Gln Lys Leu Tyr Ser Ser Lys Asp
                245                 250                 255

Thr Thr Lys Arg Pro Val Thr Thr Thr Lys Arg Glu Val Asn Ser Ala
            260                 265                 270

Val Asn Leu Asn Leu Trp Ser Trp Glu Pro Gly
        275                 280


<210> 16
<211> 318
<212> PRT
<213> Homo sapiens

<400> 16
Met Ala Leu Met Leu Ser Leu Val Leu Ser Leu Leu Lys Leu Gly Ser
  1               5                  10                  15

Gly Gln Trp Gln Val Phe Gly Pro Asp Lys Pro Val Gln Ala Leu Val
            20                  25                  30

Gly Glu Asp Ala Ala Phe Ser Cys Phe Leu Ser Pro Lys Thr Asn Ala
        35                  40                  45

Glu Ala Met Glu Val Arg Phe Phe Arg Gly Gln Phe Ser Ser Val Val
    50                  55                  60

His Leu Tyr Arg Asp Gly Lys Asp Gln Pro Phe Met Gln Met Pro Gln
 65                  70                  75                  80

Tyr Gln Gly Arg Thr Lys Leu Val Lys Asp Ser Ile Ala Glu Gly Arg
                85                  90                  95

Ile Ser Leu Arg Leu Glu Asn Ile Thr Val Leu Asp Ala Gly Leu Tyr
            100                 105                 110

Gly Cys Arg Ile Ser Ser Gln Ser Tyr Tyr Gln Lys Ala Ile Trp Glu
        115                 120                 125

Leu Gln Val Ser Ala Leu Gly Ser Val Pro Leu Ile Ser Ile Ala Gly
    130                 135                 140

Tyr Val Asp Arg Asp Ile Gln Leu Leu Cys Gln Ser Ser Gly Trp Phe
145                 150                 155                 160

Pro Arg Pro Thr Ala Lys Trp Lys Gly Pro Gln Gly Gln Asp Leu Ser
                165                 170                 175

Thr Asp Ser Arg Thr Asn Arg Asp Met His Gly Leu Phe Asp Val Glu
```

```
            180                 185                 190

Ile Ser Leu Thr Val Gln Glu Asn Ala Gly Ser Ile Ser Cys Ser Met
        195                 200                 205

Arg His Ala His Leu Ser Arg Glu Val Glu Ser Arg Val Gln Ile Gly
    210                 215                 220

Asp Trp Arg Arg Lys His Gly Gln Ala Gly Lys Arg Lys Tyr Ser Ser
225                 230                 235                 240

Ser His Ile Tyr Asp Ser Phe Pro Ser Leu Ser Phe Met Asp Phe Tyr
                245                 250                 255

Ile Leu Arg Pro Val Gly Pro Cys Arg Ala Lys Leu Val Met Gly Thr
            260                 265                 270

Leu Lys Leu Gln Ile Leu Gly Glu Val His Phe Val Glu Lys Pro His
        275                 280                 285

Ser Leu Leu Gln Ile Ser Gly Gly Ser Thr Thr Leu Lys Lys Gly Pro
    290                 295                 300

Asn Pro Trp Ser Phe Pro Ser Pro Cys Ala Leu Phe Pro Thr
305                 310                 315


<210> 17
<211> 454
<212> PRT
<213> Homo sapiens

<400> 17
Met Glu Pro Ala Ala Ala Leu His Phe Ser Arg Pro Ala Ser Leu Leu
 1               5                   10                  15

Leu Leu Leu Ser Leu Cys Ala Leu Val Ser Ala Gln Phe Thr Val Val
            20                  25                  30

Gly Pro Ala Asn Pro Ile Leu Ala Met Val Gly Glu Asn Thr Thr Leu
        35                  40                  45

Arg Cys His Leu Ser Pro Glu Lys Asn Ala Glu Asp Met Glu Val Arg
    50                  55                  60

Trp Phe Arg Ser Gln Phe Ser Pro Ala Val Phe Val Tyr Lys Gly Gly
65                  70                  75                  80

Arg Glu Arg Thr Glu Glu Gln Met Glu Glu Tyr Arg Gly Arg Ile Thr
                85                  90                  95

Phe Val Ser Lys Asp Ile Asn Arg Gly Ser Val Ala Leu Val Ile His
            100                 105                 110

Asn Val Thr Ala Gln Glu Asn Gly Ile Tyr Arg Cys Tyr Phe Gln Glu
        115                 120                 125

Gly Arg Ser Tyr Asp Glu Ala Ile Leu Arg Leu Val Val Ala Gly Leu
    130                 135                 140

Gly Ser Lys Pro Leu Ile Glu Ile Lys Ala Gln Glu Asp Gly Ser Ile
```

```
145                 150                 155                 160

Trp Leu Glu Cys Ile Ser Gly Gly Trp Tyr Pro Glu Pro Leu Thr Val
                165                 170                 175

Trp Arg Asp Pro Tyr Gly Glu Val Val Pro Ala Leu Lys Glu Val Ser
            180                 185                 190

Ile Ala Asp Ala Asp Gly Leu Phe Met Val Thr Thr Ala Val Ile Ile
        195                 200                 205

Arg Asp Lys Tyr Val Arg Asn Val Ser Cys Ser Val Asn Asn Thr Leu
    210                 215                 220

Leu Gly Gln Glu Lys Glu Thr Val Ile Phe Ile Pro Glu Ser Phe Met
225                 230                 235                 240

Pro Ser Ala Ser Pro Trp Met Val Ala Leu Ala Val Ile Leu Thr Ala
                245                 250                 255

Ser Pro Trp Met Val Ser Met Thr Val Ile Leu Ala Val Phe Ile Ile
            260                 265                 270

Phe Met Ala Val Ser Ile Cys Cys Ile Lys Lys Leu Gln Arg Glu Lys
        275                 280                 285

Lys Ile Leu Ser Gly Glu Lys Lys Val Glu Gln Glu Glu Lys Glu Ile
    290                 295                 300

Ala Gln Gln Leu Gln Glu Glu Leu Arg Trp Arg Arg Thr Phe Leu His
305                 310                 315                 320

Ala Ala Asp Val Val Leu Asp Pro Asp Thr Ala His Pro Glu Leu Phe
                325                 330                 335

Leu Ser Glu Asp Arg Arg Ser Val Arg Arg Gly Pro Tyr Arg Gln Arg
            340                 345                 350

Val Pro Asp Asn Pro Glu Arg Phe Asp Ser Gln Pro Cys Val Leu Gly
        355                 360                 365

Trp Glu Ser Phe Ala Ser Gly Lys His Tyr Arg Gly Asn Phe Thr Glu
    370                 375                 380

Trp Gly Pro Thr Arg Ala Tyr Arg Ile Asn Ser Leu Asp Ser Gln Pro
385                 390                 395                 400

Cys Arg Lys Pro Trp Pro Ser Gln Gln Pro Pro His Asn Pro Pro Asn
                405                 410                 415

Glu Arg His Ala Leu Leu Pro Ser Gly His Val Arg Glu His Leu Pro
            420                 425                 430

Ala Ala Phe Phe Thr Pro Thr Pro Ala Leu Cys Pro Ser Phe Leu Leu
        435                 440                 445

Leu Thr Ser Leu Trp Leu
    450
```

<210> 18

<211> 414
<212> PRT
<213> Homo sapiens

<400> 18

```
Met Arg Glu Ile Val Trp Tyr Arg Val Thr Asp Gly Gly Thr Ile Lys
1               5                   10                  15

Gln Lys Ile Phe Thr Phe Asp Ala Met Phe Ser Thr Asn Tyr Ser His
            20                  25                  30

Met Glu Asn Tyr Arg Lys Arg Glu Asp Leu Val Tyr Gln Ser Thr Val
        35                  40                  45

Arg Leu Pro Glu Val Arg Ile Ser Asp Asn Gly Pro Tyr Glu Cys His
    50                  55                  60

Val Gly Ile Tyr Asp Arg Ala Thr Arg Glu Lys Val Val Leu Ala Ser
65                  70                  75                  80

Gly Asn Ile Phe Leu Asn Val Met Ala Pro Pro Thr Ser Ile Glu Val
                85                  90                  95

Val Ala Ala Asp Thr Pro Ala Pro Phe Ser Arg Tyr Gln Ala Gln Asn
            100                 105                 110

Phe Thr Leu Val Cys Ile Val Ser Gly Gly Lys Pro Ala Pro Met Val
        115                 120                 125

Tyr Phe Lys Arg Asp Gly Glu Pro Ile Asp Ala Val Pro Leu Ser Glu
    130                 135                 140

Pro Pro Ala Ala Ser Ser Gly Pro Leu Gln Asp Ser Arg Pro Phe Arg
145                 150                 155                 160

Ser Leu Leu His Arg Asp Leu Asp Asp Thr Lys Met Gln Lys Ser Leu
                165                 170                 175

Ser Leu Leu Asp Ala Glu Asn Arg Gly Gly Arg Pro Tyr Thr Glu Arg
            180                 185                 190

Pro Ser Arg Gly Leu Thr Pro Asp Pro Asn Ile Leu Leu Gln Pro Thr
        195                 200                 205

Thr Glu Asn Ile Pro Glu Thr Val Val Ser Arg Glu Phe Pro Arg Trp
    210                 215                 220

Val His Ser Ala Glu Pro Thr Tyr Phe Leu Arg His Ser Arg Thr Pro
225                 230                 235                 240

Ser Ser Asp Gly Thr Val Glu Val Arg Ala Leu Leu Thr Trp Thr Leu
                245                 250                 255

Asn Pro Gln Ile Asp Asn Glu Ala Leu Phe Ser Cys Glu Val Lys His
            260                 265                 270

Pro Ala Leu Ser Met Pro Met Gln Ala Glu Val Thr Leu Val Ala Pro
        275                 280                 285

Lys Gly Pro Lys Ile Val Met Thr Pro Ser Arg Ala Arg Val Gly Asp
    290                 295                 300
```

Thr Val Arg Ile Leu Val His Gly Phe Gln Asn Glu Val Phe Pro Glu
305 310 315 320

Pro Met Phe Thr Trp Thr Arg Val Gly Ser Arg Leu Leu Asp Gly Ser
325 330 335

Ala Glu Phe Asp Gly Lys Glu Leu Val Leu Glu Arg Val Pro Ala Glu
340 345 350

Leu Asn Gly Ser Met Tyr Arg Cys Thr Ala Gln Asn Pro Leu Gly Ser
355 360 365

Thr Asp Thr His Thr Arg Leu Ile Val Phe Glu Asn Pro Asn Ile Pro
370 375 380

Arg Gly Thr Glu Asp Ser Asn Gly Ser Ile Gly Pro Thr Gly Ala Arg
385 390 395 400

Leu Thr Leu Val Leu Ala Leu Thr Val Ile Leu Glu Leu Thr
405 410

<210> 19
<211> 159
<212> PRT
<213> Homo sapiens

<400> 19
Met Glu Pro Ala Ala Ala Leu His Phe Ser Arg Pro Ala Ser Leu Leu
1 5 10 15

Leu Leu Leu Ser Leu Cys Ala Leu Val Ser Ala Gln Val Thr Val Val
20 25 30

Gly Pro Thr Asp Pro Ile Leu Ala Met Val Gly Glu Asn Thr Thr Leu
35 40 45

Arg Cys Cys Leu Ser Pro Glu Glu Asn Ala Glu Asp Met Glu Val Arg
50 55 60

Trp Phe Gln Ser Gln Phe Ser Pro Ala Val Phe Val Tyr Lys Gly Gly
65 70 75 80

Arg Glu Arg Thr Glu Glu Gln Lys Glu Glu Tyr Arg Gly Arg Thr Thr
85 90 95

Phe Val Ser Lys Asp Ser Arg Gly Ser Val Ala Leu Ile Ile His Asn
100 105 110

Val Thr Ala Glu Asp Asn Gly Ile Tyr Gln Cys Tyr Phe Gln Glu Gly
115 120 125

Arg Ser Cys Asn Glu Ala Ile Leu His Leu Val Val Ala Asp Gln His
130 135 140

Asn Pro Leu Ser Trp Ile Pro Ile Pro Gln Gly Thr Leu Ser Leu
145 150 155

<210> 20

<211> 461
<212> PRT
<213> Homo sapiens

<400> 20
Met Ala Leu Met Leu Ser Leu Val Leu Ser Leu Leu Lys Leu Gly Ser
1   5   10   15

Gly Gln Trp Gln Val Phe Gly Pro Asp Lys Pro Val Gln Ala Leu Val
            20   25   30

Gly Glu Asp Ala Ala Phe Ser Cys Phe Leu Ser Pro Lys Thr Asn Ala
        35   40   45

Glu Ala Met Glu Val Arg Phe Phe Arg Gly Gln Phe Ser Ser Val Val
    50   55   60

His Leu Tyr Arg Asp Gly Lys Asp Gln Pro Phe Met Gln Met Pro Gln
65   70   75   80

Tyr Gln Gly Arg Thr Lys Leu Val Lys Asp Ser Ile Ala Glu Gly Arg
                85   90   95

Ile Ser Leu Arg Leu Glu Asn Ile Thr Val Leu Asp Ala Gly Leu Tyr
            100   105   110

Gly Cys Arg Ile Ser Ser Gln Ser Tyr Tyr Gln Lys Ala Ile Trp Glu
        115   120   125

Leu Gln Val Ser Ala Leu Gly Ser Val Pro Leu Ile Ser Ile Thr Gly
    130   135   140

Tyr Val Asp Arg Asp Ile Gln Leu Leu Cys Gln Ser Ser Gly Trp Phe
145   150   155   160

Pro Arg Pro Thr Ala Lys Trp Lys Gly Pro Gln Gly Gln Asp Leu Ser
                165   170   175

Thr Asp Ser Arg Thr Asn Arg Asp Met His Gly Leu Phe Asp Val Glu
            180   185   190

Ile Ser Leu Thr Val Gln Glu Asn Ala Gly Ser Ile Ser Cys Ser Met
        195   200   205

Arg His Ala His Leu Ser Arg Glu Val Glu Ser Arg Val Gln Ile Gly
    210   215   220

Asp Thr Phe Phe Glu Pro Ile Ser Trp His Leu Ala Thr Lys Val Leu
225   230   235   240

Gly Ile Leu Cys Cys Gly Leu Phe Phe Gly Ile Val Gly Leu Lys Ile
                245   250   255

Phe Phe Ser Lys Phe Gln Trp Lys Ile Gln Ala Glu Leu Asp Trp Arg
            260   265   270

Arg Lys His Gly Gln Ala Glu Leu Arg Asp Ala Arg Lys His Ala Val
        275   280   285

Glu Val Thr Leu Asp Pro Glu Thr Ala His Pro Lys Leu Cys Val Ser
    290   295   300

Asp Leu Lys Thr Val Thr His Arg Lys Ala Pro Gln Glu Val Pro His
305 310 315 320

Ser Glu Lys Arg Phe Thr Arg Lys Ser Val Val Ala Ser Gln Ser Phe
325 330 335

Gln Ala Gly Lys His Tyr Trp Glu Val Asp Gly Gly His Asn Lys Arg
340 345 350

Trp Arg Val Gly Val Cys Arg Asp Asp Val Asp Arg Arg Lys Glu Tyr
355 360 365

Val Thr Leu Ser Pro Asp His Gly Tyr Trp Val Leu Arg Leu Asn Gly
370 375 380

Glu His Leu Tyr Phe Thr Leu Asn Pro Arg Phe Ile Ser Val Phe Pro
385 390 395 400

Arg Thr Pro Pro Thr Lys Ile Gly Val Phe Leu Asp Tyr Glu Cys Gly
405 410 415

Thr Ile Ser Phe Phe Asn Ile Asn Asp Gln Ser Leu Ile Tyr Thr Leu
420 425 430

Thr Cys Arg Phe Glu Gly Leu Leu Arg Pro Tyr Ile Glu Tyr Pro Ser
435 440 445

Tyr Asn Glu Gln Asn Gly Thr Pro Arg Asp Lys Gln Gln
450 455 460

<210> 21
<211> 13
<212> PRT
<213> Homo sapiens

<400> 21
Met Ala Ser Leu Gly Gln Ile Leu Phe Trp Ser Ile Ile
1 5 10

<210> 22
<211> 23
<212> PRT
<213> Homo sapiens

<400> 22
Leu Phe Leu Leu Leu Glu Ile Ser Thr His Leu Cys Phe Trp Lys Ser
1 5 10 15

Leu Arg Lys Leu Glu Gly Lys
20

<210> 23
<211> 93
<212> PRT
<213> Homo sapiens

<220>

<221> SITE
<222> (89)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (92)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 23
Met Ile Phe Leu Leu Leu Met Leu Ser Leu Glu Leu Gln Leu His Gln
1 5 10 15

Ile Ala Ala Leu Phe Thr Val Thr Val Pro Lys Glu Leu Tyr Ile Ile
20 25 30

Glu His Gly Ser Asn Val Thr Leu Glu Cys Asn Phe Asp Thr Gly Ser
35 40 45

His Val Asn Leu Gly Ala Ile Thr Ala Ser Leu Gln Lys Val Glu Asn
50 55 60

Asp Thr Ser Pro His Arg Glu Arg Ala Thr Leu Leu Glu Glu Gln Leu
65 70 75 80

Pro Leu Gly Lys Ala Ser Phe Pro Xaa Leu Lys Xaa Lys
85 90

<210> 24
<211> 461
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (234)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (236)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 24
Met Ala Leu Met Leu Ser Leu Val Leu Ser Leu Leu Lys Leu Gly Ser
1 5 10 15

Gly Gln Trp Gln Val Phe Gly Pro Asp Lys Pro Val Gln Ala Leu Val
20 25 30

Gly Glu Asp Ala Ala Phe Ser Cys Phe Leu Ser Pro Lys Thr Asn Ala
35 40 45

Glu Ala Met Glu Val Arg Phe Phe Arg Gly Gln Phe Ser Ser Val Val
50 55 60

His Leu Tyr Arg Asp Gly Lys Asp Gln Pro Phe Met Gln Met Pro Gln
65 70 75 80

Tyr Gln Gly Arg Thr Lys Leu Val Lys Asp Ser Ile Ala Glu Gly Arg

85 90 95

Ile Ser Leu Arg Leu Glu Asn Ile Thr Val Leu Asp Ala Gly Leu Tyr
100 105 110

Gly Cys Arg Ile Ser Ser Gln Ser Tyr Tyr Gln Lys Ala Ile Trp Glu
115 120 125

Leu Gln Val Ser Ala Leu Gly Ser Val Pro Leu Ile Ser Ile Thr Gly
130 135 140

Tyr Val Asp Arg Asp Ile Gln Leu Leu Cys Gln Ser Ser Gly Trp Phe
145 150 155 160

Pro Arg Pro Thr Ala Lys Trp Lys Gly Pro Gln Gly Gln Asp Leu Ser
165 170 175

Thr Asp Ser Arg Thr Asn Arg Asp Met His Gly Leu Phe Asp Val Glu
180 185 190

Ile Ser Leu Thr Val Gln Glu Asn Ala Gly Ser Ile Ser Cys Ser Met
195 200 205

Arg His Ala His Leu Ser Arg Glu Val Glu Ser Arg Val Gln Ile Gly
210 215 220

Asp Thr Phe Phe Glu Pro Ile Ser Trp Xaa Leu Xaa Thr Lys Val Leu
225 230 235 240

Gly Ile Leu Cys Cys Gly Leu Phe Phe Gly Ile Val Gly Leu Lys Ile
245 250 255

Phe Phe Ser Lys Phe Gln Trp Lys Ile Gln Ala Glu Leu Asp Trp Arg
260 265 270

Arg Lys His Gly Gln Ala Glu Leu Arg Asp Ala Arg Lys His Ala Val
275 280 285

Glu Val Thr Leu Asp Pro Glu Thr Ala His Pro Lys Leu Cys Val Ser
290 295 300

Asp Leu Lys Thr Val Thr His Arg Lys Ala Pro Gln Glu Val Pro His
305 310 315 320

Ser Glu Lys Arg Phe Thr Arg Lys Ser Val Val Ala Ser Gln Ser Phe
325 330 335

Gln Ala Gly Lys His Tyr Trp Glu Val Asp Gly Gly His Asn Lys Arg
340 345 350

Trp Arg Val Gly Val Cys Arg Asp Asp Val Asp Arg Arg Lys Glu Tyr
355 360 365

Val Thr Leu Ser Pro Asp His Gly Tyr Trp Val Leu Arg Leu Asn Gly
370 375 380

Glu His Leu Tyr Phe Thr Leu Asn Pro Arg Phe Ile Ser Val Phe Pro
385 390 395 400

Arg Thr Pro Pro Thr Lys Ile Gly Val Phe Leu Asp Tyr Glu Cys Gly
405 410 415

Thr Ile Ser Phe Phe Asn Ile Asn Asp Gln Ser Leu Ile Tyr Thr Leu
420 425 430

Thr Cys Arg Phe Glu Gly Leu Leu Arg Pro Tyr Ile Glu Tyr Pro Ser
435 440 445

Tyr Asn Glu Gln Asn Gly Thr Pro Arg Asp Lys Gln Gln
450 455 460

<210> 25
<211> 402
<212> PRT
<213> Homo sapiens

<400> 25
Met Glu Pro Ala Ala Ala Leu His Phe Ser Arg Pro Ala Ser Leu Leu
1 5 10 15

Leu Leu Leu Ser Leu Cys Ala Leu Val Ser Ala Gln Phe Thr Val Val
20 25 30

Gly Pro Ala Asn Pro Ile Leu Ala Met Val Gly Glu Asn Thr Thr Leu
35 40 45

Arg Cys His Leu Ser Pro Glu Lys Asn Ala Glu Asp Met Glu Val Arg
50 55 60

Trp Phe Arg Ser Gln Phe Ser Pro Ala Val Phe Val Tyr Lys Gly Gly
65 70 75 80

Arg Glu Arg Thr Glu Glu Gln Met Glu Glu Tyr Arg Gly Arg Ile Thr
85 90 95

Phe Val Ser Lys Asp Ile Asn Arg Gly Ser Val Ala Leu Val Ile His
100 105 110

Asn Val Thr Ala Gln Glu Asn Gly Ile Tyr Arg Cys Tyr Phe Gln Glu
115 120 125

Gly Arg Ser Tyr Asp Glu Ala Ile Leu Arg Leu Val Val Ala Gly Leu
130 135 140

Gly Ser Lys Pro Leu Ile Glu Ile Lys Ala Gln Glu Asp Gly Ser Ile
145 150 155 160

Trp Leu Glu Cys Ile Ser Gly Gly Trp Tyr Pro Glu Pro Leu Thr Val
165 170 175

Trp Arg Asp Pro Tyr Gly Glu Val Val Pro Ala Leu Lys Glu Val Ser
180 185 190

Ile Ala Asp Ala Asp Gly Leu Phe Met Val Thr Thr Ala Val Ile Ile
195 200 205

Arg Asp Lys Tyr Val Arg Asn Val Ser Cys Ser Val Asn Asn Thr Leu
210 215 220

Leu Gly Gln Glu Lys Glu Thr Val Ile Phe Ile Pro Glu Ser Phe Met
225 230 235 240

Pro Ser Ala Ser Pro Trp Met Val Ala Leu Ala Val Ile Leu Thr Ala
245 250 255

Ser Pro Trp Met Val Ser Met Thr Val Ile Leu Ala Val Phe Ile Ile
260 265 270

Phe Met Ala Val Ser Ile Cys Cys Ile Lys Lys Leu Gln Arg Glu Lys
275 280 285

Lys Ile Leu Ser Gly Glu Lys Lys Val Glu Gln Glu Glu Lys Glu Ile
290 295 300

Ala Gln Gln Leu Gln Glu Glu Leu Arg Trp Arg Arg Thr Phe Leu His
305 310 315 320

Ala Ala Asp Val Val Leu Asp Pro Asp Thr Ala His Pro Glu Leu Phe
325 330 335

Leu Ser Glu Asp Arg Arg Ser Val Arg Arg Gly Pro Tyr Arg Gln Arg
340 345 350

Val Pro Asp Asn Pro Glu Arg Phe Asp Ser Gln Pro Cys Val Leu Gly
355 360 365

Trp Glu Ser Phe Ala Ser Gly Lys His Tyr Arg Gly Asn Phe Thr Glu
370 375 380

Trp Gly Pro Thr Arg Ala Tyr Arg Ile Asn Ser Leu Asp Ser Gln Pro
385 390 395 400

Cys Arg

<210> 26
<211> 20
<212> PRT
<213> Homo sapiens

<400> 26
Ser Lys Ala Ser Leu Cys Val Ser Ser Phe Phe Ala Ile Ser Trp Ala
1 5 10 15

Leu Leu Pro Leu
20

<210> 27
<211> 255
<212> PRT
<213> Homo sapiens

<400> 27
Met Ala Ser Leu Gly Gln Ile Leu Phe Trp Ser Ile Ile Ser Ile Ile
1 5 10 15

Ile Ile Leu Ala Gly Ala Ile Ala Leu Ile Ile Gly Phe Gly Ile Ser
20 25 30

Gly Arg His Ser Ile Thr Val Thr Thr Val Ala Ser Ala Gly Asn Ile

35 40 45

Gly Glu Asp Gly Ile Leu Ser Cys Thr Phe Glu Pro Asp Ile Lys Leu
50 55 60

Ser Asp Ile Val Ile Gln Trp Leu Lys Glu Gly Val Leu Gly Leu Val
65 70 75 80

His Glu Phe Lys Glu Gly Lys Asp Glu Leu Ser Glu Gln Asp Glu Met
85 90 95

Phe Arg Gly Arg Thr Ala Val Phe Ala Asp Gln Val Ile Val Gly Asn
100 105 110

Ala Ser Leu Arg Leu Lys Asn Val Gln Leu Thr Asp Ala Gly Thr Tyr
115 120 125

Lys Cys Tyr Ile Ile Thr Ser Lys Gly Lys Gly Asn Ala Asn Leu Glu
130 135 140

Tyr Lys Thr Gly Ala Phe Ser Met Pro Glu Val Asn Val Asp Tyr Asn
145 150 155 160

Ala Ser Ser Glu Thr Leu Arg Cys Glu Ala Pro Arg Trp Phe Pro Gln
165 170 175

Pro Thr Val Val Trp Ala Ser Gln Val Asp Gln Gly Ala Asn Phe Ser
180 185 190

Glu Val Ser Asn Thr Ser Phe Glu Leu Asn Ser Glu Asn Val Thr Met
195 200 205

Lys Val Val Ser Val Leu Tyr Asn Val Thr Ile Asn Asn Thr Tyr Ser
210 215 220

Cys Met Ile Glu Asn Asp Ile Ala Lys Ala Thr Gly Asp Ile Lys Val
225 230 235 240

Thr Glu Ser Glu Ile Lys Arg Arg Ser His Leu Gln Leu Leu Asn
245 250 255

<210> 28
<211> 231
<212> PRT
<213> Homo sapiens

<400> 28
Leu Ile Ile Gly Phe Gly Ile Ser Gly Arg His Ser Ile Thr Val Thr
1 5 10 15

Thr Val Ala Ser Ala Gly Asn Ile Gly Glu Asp Gly Ile Leu Ser Cys
20 25 30

Thr Phe Glu Pro Asp Ile Lys Leu Ser Asp Ile Val Ile Gln Trp Leu
35 40 45

Lys Glu Gly Val Leu Gly Leu Val His Glu Phe Lys Glu Gly Lys Asp
50 55 60

Glu Leu Ser Glu Gln Asp Glu Met Phe Arg Gly Arg Thr Ala Val Phe

65 70 75 80

Ala Asp Gln Val Ile Val Gly Asn Ala Ser Leu Arg Leu Lys Asn Val
85 90 95

Gln Leu Thr Asp Ala Gly Thr Tyr Lys Cys Tyr Ile Ile Thr Ser Lys
100 105 110

Gly Lys Gly Asn Ala Asn Leu Glu Tyr Lys Thr Gly Ala Phe Ser Met
115 120 125

Pro Glu Val Asn Val Asp Tyr Asn Ala Ser Ser Glu Thr Leu Arg Cys
130 135 140

Glu Ala Pro Arg Trp Phe Pro Gln Pro Thr Val Val Trp Ala Ser Gln
145 150 155 160

Val Asp Gln Gly Ala Asn Phe Ser Glu Val Ser Asn Thr Ser Phe Glu
165 170 175

Leu Asn Ser Glu Asn Val Thr Met Lys Val Val Ser Val Leu Tyr Asn
180 185 190

Val Thr Ile Asn Asn Thr Tyr Ser Cys Met Ile Glu Asn Asp Ile Ala
195 200 205

Lys Ala Thr Gly Asp Ile Lys Val Thr Glu Ser Glu Ile Lys Arg Arg
210 215 220

Ser His Leu Gln Leu Leu Asn
225 230

<210> 29
<211> 24
<212> PRT
<213> Homo sapiens

<400> 29
Met Ala Ser Leu Gly Gln Ile Leu Phe Trp Ser Ile Ile Ser Ile Ile
1 5 10 15

Ile Ile Leu Ala Gly Ala Ile Ala
20

<210> 30
<211> 30
<212> PRT
<213> Homo sapiens

<400> 30
Pro Thr Trp Leu Leu His Ile Phe Ile Pro Ser Cys Ile Ile Ala Phe
1 5 10 15

Ile Phe Ile Ala Thr Val Ile Ala Leu Arg Lys Gln Leu Cys
20 25 30

<210> 31
<211> 218

```
<212> PRT
<213> Homo sapiens

<400> 31
Met Ile Phe Leu Leu Leu Met Leu Ser Leu Glu Leu Gln Leu His Gln
 1               5                   10                  15

Ile Ala Ala Leu Phe Thr Val Thr Val Pro Lys Glu Leu Tyr Ile Ile
            20                  25                  30

Glu His Gly Ser Asn Val Thr Leu Glu Cys Asn Phe Asp Thr Gly Ser
        35                  40                  45

His Val Asn Leu Gly Ala Ile Thr Ala Ser Leu Gln Lys Val Glu Asn
    50                  55                  60

Asp Thr Ser Pro His Arg Glu Arg Ala Thr Leu Leu Glu Glu Gln Leu
65                  70                  75                  80

Pro Leu Gly Lys Ala Ser Phe His Ile Pro Gln Val Gln Val Arg Asp
                85                  90                  95

Glu Gly Gln Tyr Gln Cys Ile Ile Ile Tyr Gly Val Ala Trp Asp Tyr
            100                 105                 110

Lys Tyr Leu Thr Leu Lys Val Lys Ala Ser Tyr Arg Lys Ile Asn Thr
        115                 120                 125

His Ile Leu Lys Val Pro Glu Thr Asp Glu Val Glu Leu Thr Cys Gln
    130                 135                 140

Ala Thr Gly Tyr Pro Leu Ala Glu Val Ser Trp Pro Asn Val Ser Val
145                 150                 155                 160

Pro Ala Asn Thr Ser His Ser Arg Thr Pro Glu Gly Leu Tyr Gln Val
                165                 170                 175

Thr Ser Val Leu Arg Leu Lys Pro Pro Pro Gly Arg Asn Phe Ser Cys
            180                 185                 190

Val Phe Trp Asn Thr His Val Arg Glu Leu Thr Leu Ala Ser Ile Asp
        195                 200                 205

Leu Gln Ser Gln Met Glu Pro Arg Thr His
    210                 215


<210> 32
<211> 199
<212> PRT
<213> Homo sapiens

<400> 32
Leu Phe Thr Val Thr Val Pro Lys Glu Leu Tyr Ile Ile Glu His Gly
 1               5                   10                  15

Ser Asn Val Thr Leu Glu Cys Asn Phe Asp Thr Gly Ser His Val Asn
            20                  25                  30

Leu Gly Ala Ile Thr Ala Ser Leu Gln Lys Val Glu Asn Asp Thr Ser
        35                  40                  45
```

Pro His Arg Glu Arg Ala Thr Leu Leu Glu Glu Gln Leu Pro Leu Gly
50 55 60

Lys Ala Ser Phe His Ile Pro Gln Val Gln Val Arg Asp Glu Gly Gln
65 70 75 80

Tyr Gln Cys Ile Ile Ile Tyr Gly Val Ala Trp Asp Tyr Lys Tyr Leu
85 90 95

Thr Leu Lys Val Lys Ala Ser Tyr Arg Lys Ile Asn Thr His Ile Leu
100 105 110

Lys Val Pro Glu Thr Asp Glu Val Glu Leu Thr Cys Gln Ala Thr Gly
115 120 125

Tyr Pro Leu Ala Glu Val Ser Trp Pro Asn Val Ser Val Pro Ala Asn
130 135 140

Thr Ser His Ser Arg Thr Pro Glu Gly Leu Tyr Gln Val Thr Ser Val
145 150 155 160

Leu Arg Leu Lys Pro Pro Pro Gly Arg Asn Phe Ser Cys Val Phe Trp
165 170 175

Asn Thr His Val Arg Glu Leu Thr Leu Ala Ser Ile Asp Leu Gln Ser
180 185 190

Gln Met Glu Pro Arg Thr His
195

<210> 33
<211> 19
<212> PRT
<213> Homo sapiens

<400> 33
Met Ile Phe Leu Leu Leu Met Leu Ser Leu Glu Leu Gln Leu His Gln
1 5 10 15

Ile Ala Ala

<210> 34
<211> 93
<212> PRT
<213> Homo sapiens

<400> 34
Glu Leu Tyr Ile Ile Glu His Gly Ser Asn Val Thr Leu Glu Cys Asn
1 5 10 15

Phe Asp Thr Gly Ser His Val Asn Leu Gly Ala Ile Thr Ala Ser Leu
20 25 30

Gln Lys Val Glu Asn Asp Thr Ser Pro His Arg Glu Arg Ala Thr Leu
35 40 45

Leu Glu Glu Gln Leu Pro Leu Gly Lys Ala Ser Phe His Ile Pro Gln

50 55 60

Val Gln Val Arg Asp Glu Gly Gln Tyr Gln Cys Ile Ile Ile Tyr Gly
65 70 75 80

Val Ala Trp Asp Tyr Lys Tyr Leu Thr Leu Lys Val Lys
85 90

<210> 35
<211> 94
<212> PRT
<213> Homo sapiens

<400> 35
Ser Tyr Arg Lys Ile Asn Thr His Ile Leu Lys Val Pro Glu Thr Asp
1 5 10 15

Glu Val Glu Leu Thr Cys Gln Ala Thr Gly Tyr Pro Leu Ala Glu Val
20 25 30

Ser Trp Pro Asn Val Ser Val Pro Ala Asn Thr Ser His Ser Arg Thr
35 40 45

Pro Glu Gly Leu Tyr Gln Val Thr Ser Val Leu Arg Leu Lys Pro Pro
50 55 60

Pro Gly Arg Asn Phe Ser Cys Val Phe Trp Asn Thr His Val Arg Glu
65 70 75 80

Leu Thr Leu Ala Ser Ile Asp Leu Gln Ser Gln Met Glu Pro
85 90

<210> 36
<211> 301
<212> PRT
<213> Homo sapiens

<400> 36
Gln Trp Gln Val Phe Gly Pro Asp Lys Pro Val Gln Ala Leu Val Gly
1 5 10 15

Glu Asp Ala Ala Phe Ser Cys Phe Leu Ser Pro Lys Thr Asn Ala Glu
20 25 30

Ala Met Glu Val Arg Phe Phe Arg Gly Gln Phe Ser Ser Val Val His
35 40 45

Leu Tyr Arg Asp Gly Lys Asp Gln Pro Phe Met Gln Met Pro Gln Tyr
50 55 60

Gln Gly Arg Thr Lys Leu Val Lys Asp Ser Ile Ala Glu Gly Arg Ile
65 70 75 80

Ser Leu Arg Leu Glu Asn Ile Thr Val Leu Asp Ala Gly Leu Tyr Gly
85 90 95

Cys Arg Ile Ser Ser Gln Ser Tyr Tyr Gln Lys Ala Ile Trp Glu Leu
100 105 110

Gln Val Ser Ala Leu Gly Ser Val Pro Leu Ile Ser Ile Ala Gly Tyr
115 120 125

Val Asp Arg Asp Ile Gln Leu Leu Cys Gln Ser Ser Gly Trp Phe Pro
130 135 140

Arg Pro Thr Ala Lys Trp Lys Gly Pro Gln Gly Gln Asp Leu Ser Thr
145 150 155 160

Asp Ser Arg Thr Asn Arg Asp Met His Gly Leu Phe Asp Val Glu Ile
165 170 175

Ser Leu Thr Val Gln Glu Asn Ala Gly Ser Ile Ser Cys Ser Met Arg
180 185 190

His Ala His Leu Ser Arg Glu Val Glu Ser Arg Val Gln Ile Gly Asp
195 200 205

Trp Arg Arg Lys His Gly Gln Ala Gly Lys Arg Lys Tyr Ser Ser Ser
210 215 220

His Ile Tyr Asp Ser Phe Pro Ser Leu Ser Phe Met Asp Phe Tyr Ile
225 230 235 240

Leu Arg Pro Val Gly Pro Cys Arg Ala Lys Leu Val Met Gly Thr Leu
245 250 255

Lys Leu Gln Ile Leu Gly Glu Val His Phe Val Glu Lys Pro His Ser
260 265 270

Leu Leu Gln Ile Ser Gly Gly Ser Thr Thr Leu Lys Lys Gly Pro Asn
275 280 285

Pro Trp Ser Phe Pro Ser Pro Cys Ala Leu Phe Pro Thr
290 295 300

<210> 37
<211> 17
<212> PRT
<213> Homo sapiens

<400> 37
Met Ala Leu Met Leu Ser Leu Val Leu Ser Leu Leu Lys Leu Gly Ser
1 5 10 15

Gly

<210> 38
<211> 26
<212> PRT
<213> Homo sapiens

<400> 38
Thr Ala Ser Pro Trp Met Val Ser Met Thr Val Ile Leu Ala Val Phe
1 5 10 15

Ile Ile Phe Met Ala Val Ser Ile Cys Cys
20 25

<210> 39
<211> 254
<212> PRT
<213> Homo sapiens

<400> 39
```
Met Glu Pro Ala Ala Ala Leu His Phe Ser Arg Pro Ala Ser Leu Leu
 1               5                  10                  15

Leu Leu Leu Ser Leu Cys Ala Leu Val Ser Ala Gln Phe Thr Val Val
            20                  25                  30

Gly Pro Ala Asn Pro Ile Leu Ala Met Val Gly Glu Asn Thr Thr Leu
        35                  40                  45

Arg Cys His Leu Ser Pro Glu Lys Asn Ala Glu Asp Met Glu Val Arg
    50                  55                  60

Trp Phe Arg Ser Gln Phe Ser Pro Ala Val Phe Val Tyr Lys Gly Gly
65                  70                  75                  80

Arg Glu Arg Thr Glu Glu Gln Met Glu Glu Tyr Arg Gly Arg Ile Thr
                85                  90                  95

Phe Val Ser Lys Asp Ile Asn Arg Gly Ser Val Ala Leu Val Ile His
            100                 105                 110

Asn Val Thr Ala Gln Glu Asn Gly Ile Tyr Arg Cys Tyr Phe Gln Glu
        115                 120                 125

Gly Arg Ser Tyr Asp Glu Ala Ile Leu Arg Leu Val Val Ala Gly Leu
    130                 135                 140

Gly Ser Lys Pro Leu Ile Glu Ile Lys Ala Gln Glu Asp Gly Ser Ile
145                 150                 155                 160

Trp Leu Glu Cys Ile Ser Gly Gly Trp Tyr Pro Glu Pro Leu Thr Val
                165                 170                 175

Trp Arg Asp Pro Tyr Gly Glu Val Val Pro Ala Leu Lys Glu Val Ser
            180                 185                 190

Ile Ala Asp Ala Asp Gly Leu Phe Met Val Thr Thr Ala Val Ile Ile
        195                 200                 205

Arg Asp Lys Tyr Val Arg Asn Val Ser Cys Ser Val Asn Asn Thr Leu
    210                 215                 220

Leu Gly Gln Glu Lys Glu Thr Val Ile Phe Ile Pro Glu Ser Phe Met
225                 230                 235                 240

Pro Ser Ala Ser Pro Trp Met Val Ala Leu Ala Val Ile Leu
                245                 250
```

<210> 40
<211> 227
<212> PRT
<213> Homo sapiens

<400> 40

```
Gln Phe Thr Val Val Gly Pro Ala Asn Pro Ile Leu Ala Met Val Gly
 1               5                  10                  15

Glu Asn Thr Thr Leu Arg Cys His Leu Ser Pro Glu Lys Asn Ala Glu
            20                  25                  30

Asp Met Glu Val Arg Trp Phe Arg Ser Gln Phe Ser Pro Ala Val Phe
        35                  40                  45

Val Tyr Lys Gly Gly Arg Glu Arg Thr Glu Glu Gln Met Glu Glu Tyr
    50                  55                  60

Arg Gly Arg Ile Thr Phe Val Ser Lys Asp Ile Asn Arg Gly Ser Val
65                  70                  75                  80

Ala Leu Val Ile His Asn Val Thr Ala Gln Glu Asn Gly Ile Tyr Arg
                85                  90                  95

Cys Tyr Phe Gln Glu Gly Arg Ser Tyr Asp Glu Ala Ile Leu Arg Leu
            100                 105                 110

Val Val Ala Gly Leu Gly Ser Lys Pro Leu Ile Glu Ile Lys Ala Gln
        115                 120                 125

Glu Asp Gly Ser Ile Trp Leu Glu Cys Ile Ser Gly Gly Trp Tyr Pro
    130                 135                 140

Glu Pro Leu Thr Val Trp Arg Asp Pro Tyr Gly Glu Val Val Pro Ala
145                 150                 155                 160

Leu Lys Glu Val Ser Ile Ala Asp Ala Asp Gly Leu Phe Met Val Thr
                165                 170                 175

Thr Ala Val Ile Ile Arg Asp Lys Tyr Val Arg Asn Val Ser Cys Ser
            180                 185                 190

Val Asn Asn Thr Leu Leu Gly Gln Glu Lys Glu Thr Val Ile Phe Ile
        195                 200                 205

Pro Glu Ser Phe Met Pro Ser Ala Ser Pro Trp Met Val Ala Leu Ala
    210                 215                 220

Val Ile Leu
225
```

<210> 41
<211> 27
<212> PRT
<213> Homo sapiens

<400> 41

```
Met Glu Pro Ala Ala Ala Leu His Phe Ser Arg Pro Ala Ser Leu Leu
 1               5                  10                  15

Leu Leu Leu Ser Leu Cys Ala Leu Val Ser Ala
            20                  25
```

<210> 42
<211> 20
<212> PRT
<213> Homo sapiens

<400> 42
```
Gly Pro Thr Gly Ala Arg Leu Thr Leu Val Leu Ala Leu Thr Val Ile
  1               5                  10                  15

Leu Glu Leu Thr
             20
```

<210> 43
<211> 394
<212> PRT
<213> Homo sapiens

<400> 43
```
Met Arg Glu Ile Val Trp Tyr Arg Val Thr Asp Gly Gly Thr Ile Lys
  1               5                  10                  15

Gln Lys Ile Phe Thr Phe Asp Ala Met Phe Ser Thr Asn Tyr Ser His
             20                  25                  30

Met Glu Asn Tyr Arg Lys Arg Glu Asp Leu Val Tyr Gln Ser Thr Val
         35                  40                  45

Arg Leu Pro Glu Val Arg Ile Ser Asp Asn Gly Pro Tyr Glu Cys His
     50                  55                  60

Val Gly Ile Tyr Asp Arg Ala Thr Arg Glu Lys Val Val Leu Ala Ser
 65                  70                  75                  80

Gly Asn Ile Phe Leu Asn Val Met Ala Pro Pro Thr Ser Ile Glu Val
                 85                  90                  95

Val Ala Ala Asp Thr Pro Ala Pro Phe Ser Arg Tyr Gln Ala Gln Asn
            100                 105                 110

Phe Thr Leu Val Cys Ile Val Ser Gly Gly Lys Pro Ala Pro Met Val
        115                 120                 125

Tyr Phe Lys Arg Asp Gly Glu Pro Ile Asp Ala Val Pro Leu Ser Glu
    130                 135                 140

Pro Pro Ala Ala Ser Ser Gly Pro Leu Gln Asp Ser Arg Pro Phe Arg
145                 150                 155                 160

Ser Leu Leu His Arg Asp Leu Asp Asp Thr Lys Met Gln Lys Ser Leu
                165                 170                 175

Ser Leu Leu Asp Ala Glu Asn Arg Gly Gly Arg Pro Tyr Thr Glu Arg
            180                 185                 190

Pro Ser Arg Gly Leu Thr Pro Asp Pro Asn Ile Leu Leu Gln Pro Thr
        195                 200                 205

Thr Glu Asn Ile Pro Glu Thr Val Val Ser Arg Glu Phe Pro Arg Trp
    210                 215                 220
```

Val His Ser Ala Glu Pro Thr Tyr Phe Leu Arg His Ser Arg Thr Pro
225 230 235 240

Ser Ser Asp Gly Thr Val Glu Val Arg Ala Leu Leu Thr Trp Thr Leu
245 250 255

Asn Pro Gln Ile Asp Asn Glu Ala Leu Phe Ser Cys Glu Val Lys His
260 265 270

Pro Ala Leu Ser Met Pro Met Gln Ala Glu Val Thr Leu Val Ala Pro
275 280 285

Lys Gly Pro Lys Ile Val Met Thr Pro Ser Arg Ala Arg Val Gly Asp
290 295 300

Thr Val Arg Ile Leu Val His Gly Phe Gln Asn Glu Val Phe Pro Glu
305 310 315 320

Pro Met Phe Thr Trp Thr Arg Val Gly Ser Arg Leu Leu Asp Gly Ser
325 330 335

Ala Glu Phe Asp Gly Lys Glu Leu Val Leu Glu Arg Val Pro Ala Glu
340 345 350

Leu Asn Gly Ser Met Tyr Arg Cys Thr Ala Gln Asn Pro Leu Gly Ser
355 360 365

Thr Asp Thr His Thr Arg Leu Ile Val Phe Glu Asn Pro Asn Ile Pro
370 375 380

Arg Gly Thr Glu Asp Ser Asn Gly Ser Ile
385 390

<210> 44
<211> 132
<212> PRT
<213> Homo sapiens

<400> 44
Gln Val Thr Val Val Gly Pro Thr Asp Pro Ile Leu Ala Met Val Gly
1 5 10 15

Glu Asn Thr Thr Leu Arg Cys Cys Leu Ser Pro Glu Glu Asn Ala Glu
20 25 30

Asp Met Glu Val Arg Trp Phe Gln Ser Gln Phe Ser Pro Ala Val Phe
35 40 45

Val Tyr Lys Gly Gly Arg Glu Arg Thr Glu Glu Gln Lys Glu Glu Tyr
50 55 60

Arg Gly Arg Thr Thr Phe Val Ser Lys Asp Ser Arg Gly Ser Val Ala
65 70 75 80

Leu Ile Ile His Asn Val Thr Ala Glu Asp Asn Gly Ile Tyr Gln Cys
85 90 95

Tyr Phe Gln Glu Gly Arg Ser Cys Asn Glu Ala Ile Leu His Leu Val
100 105 110

Val Ala Asp Gln His Asn Pro Leu Ser Trp Ile Pro Ile Pro Gln Gly
115 120 125

Thr Leu Ser Leu
130

<210> 45
<211> 27
<212> PRT
<213> Homo sapiens

<400> 45
Met Glu Pro Ala Ala Ala Leu His Phe Ser Arg Pro Ala Ser Leu Leu
1 5 10 15

Leu Leu Leu Ser Leu Cys Ala Leu Val Ser Ala
20 25

<210> 46
<211> 13
<212> PRT
<213> Homo sapiens

<400> 46
Leu Gly Ile Leu Cys Cys Gly Leu Phe Phe Gly Ile Val
1 5 10

<210> 47
<211> 17
<212> PRT
<213> Homo sapiens

<400> 47
Met Ala Leu Met Leu Ser Leu Val Leu Ser Leu Leu Lys Leu Gly Ser
1 5 10 15

Gly

<210> 48
<211> 239
<212> PRT
<213> Homo sapiens

<400> 48
Met Ala Leu Met Leu Ser Leu Val Leu Ser Leu Leu Lys Leu Gly Ser
1 5 10 15

Gly Gln Trp Gln Val Phe Gly Pro Asp Lys Pro Val Gln Ala Leu Val
20 25 30

Gly Glu Asp Ala Ala Phe Ser Cys Phe Leu Ser Pro Lys Thr Asn Ala
35 40 45

Glu Ala Met Glu Val Arg Phe Phe Arg Gly Gln Phe Ser Ser Val Val
50 55 60

His Leu Tyr Arg Asp Gly Lys Asp Gln Pro Phe Met Gln Met Pro Gln
65 70 75 80

Tyr Gln Gly Arg Thr Lys Leu Val Lys Asp Ser Ile Ala Glu Gly Arg
85 90 95

Ile Ser Leu Arg Leu Glu Asn Ile Thr Val Leu Asp Ala Gly Leu Tyr
100 105 110

Gly Cys Arg Ile Ser Ser Gln Ser Tyr Tyr Gln Lys Ala Ile Trp Glu
115 120 125

Leu Gln Val Ser Ala Leu Gly Ser Val Pro Leu Ile Ser Ile Thr Gly
130 135 140

Tyr Val Asp Arg Asp Ile Gln Leu Leu Cys Gln Ser Ser Gly Trp Phe
145 150 155 160

Pro Arg Pro Thr Ala Lys Trp Lys Gly Pro Gln Gly Gln Asp Leu Ser
165 170 175

Thr Asp Ser Arg Thr Asn Arg Asp Met His Gly Leu Phe Asp Val Glu
180 185 190

Ile Ser Leu Thr Val Gln Glu Asn Ala Gly Ser Ile Ser Cys Ser Met
195 200 205

Arg His Ala His Leu Ser Arg Glu Val Glu Ser Arg Val Gln Ile Gly
210 215 220

Asp Thr Phe Phe Glu Pro Ile Ser Trp His Leu Ala Thr Lys Val
225 230 235

<210> 49
<211> 222
<212> PRT
<213> Homo sapiens

<400> 49
Gln Trp Gln Val Phe Gly Pro Asp Lys Pro Val Gln Ala Leu Val Gly
1 5 10 15

Glu Asp Ala Ala Phe Ser Cys Phe Leu Ser Pro Lys Thr Asn Ala Glu
20 25 30

Ala Met Glu Val Arg Phe Phe Arg Gly Gln Phe Ser Ser Val Val His
35 40 45

Leu Tyr Arg Asp Gly Lys Asp Gln Pro Phe Met Gln Met Pro Gln Tyr
50 55 60

Gln Gly Arg Thr Lys Leu Val Lys Asp Ser Ile Ala Glu Gly Arg Ile
65 70 75 80

Ser Leu Arg Leu Glu Asn Ile Thr Val Leu Asp Ala Gly Leu Tyr Gly
85 90 95

Cys Arg Ile Ser Ser Gln Ser Tyr Tyr Gln Lys Ala Ile Trp Glu Leu
100 105 110

```
Gln Val Ser Ala Leu Gly Ser Val Pro Leu Ile Ser Ile Thr Gly Tyr
        115                 120                 125

Val Asp Arg Asp Ile Gln Leu Leu Cys Gln Ser Ser Gly Trp Phe Pro
    130                 135                 140

Arg Pro Thr Ala Lys Trp Lys Gly Pro Gln Gly Gln Asp Leu Ser Thr
145                 150                 155                 160

Asp Ser Arg Thr Asn Arg Asp Met His Gly Leu Phe Asp Val Glu Ile
                165                 170                 175

Ser Leu Thr Val Gln Glu Asn Ala Gly Ser Ile Ser Cys Ser Met Arg
            180                 185                 190

His Ala His Leu Ser Arg Glu Val Glu Ser Arg Val Gln Ile Gly Asp
        195                 200                 205

Thr Phe Phe Glu Pro Ile Ser Trp His Leu Ala Thr Lys Val
    210                 215                 220
```

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM OR OTHER BIOLOGICAL MATERIAL

(PCT Rule 13*bis*)

A. The indications made below relate to the deposited microorganism or other biological material referred to in the description at Page 115, Table 1.

B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet ☐

Name of depositary institution: American Type Culture Collection

Address of depositary institution *(including postal code and country)*
10801 University Boulevard
Manassas, Virginia 20110-2209
United States of America

Date of deposit	Accession Number
August 7, 2000	PTA-2332

C. ADDITIONAL INDICATIONS *(leave blank if not applicable)* This information is continued on an additional sheet ☐

D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE *(if the indications are not for all designated States)*

Europe
In respect of those designations in which a European Patent is sought a sample of the deposited microorganism will be made available until the publication of the mention of the grant of the European patent or until the date on which the application has been refused or withdrawn or is deemed to be withdrawn, only by the issue of such a sample to an expert nominated by the person requesting the sample (Rule 28(4) EPC).

Continued on additional sheets

E. SEPARATE FURNISHING OF INDICATIONS *(leave blank if not applicable)*

The indications listed below will be submitted to the international Bureau later *(specify the general nature of the indications e.g., "Accession Number of Deposit")*

For receiving Office use only	For International Bureau use only
☑ This sheet was received with the international application	☐ This sheet was received by the International Bureau on:
Authorized officer Vanessa E. Clark	Authorized officer

ATCC Deposit No. PTA-2332

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

ATCC Deposit No. PTA-2332

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later that at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/20917

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :C07H 21/04; C12N 15/10, 15/11, 15/12
US CL : 536/23.1, 23.5; 435/69.1, 326, 320.1, 455
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 536/23.1, 23.5; 435/69.1, 326, 320.1, 455

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WEST, DIALOG, BIOSIS, CA, EMBASE, ,MEDLINE
search terms: fiscella, ni, ruben, b7, b7-1, b7-2, cd80, cd86

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 00/36107 A (CORIXA CORPORATION) 22 JUNE 2000, see entire document, particularly SEQ ID NO: 391.	1-10, 14, 15

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
01 OCTOBER 2001	16 NOV 2001

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231
Facsimile No. (703) 305-3230

Authorized officer
PHILLIP GAMBEL
Telephone No. (703) 308-0196

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/20917

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-10, 14, 15

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Groups 1-49, claims 1-10, 14, 15, all in part, drawn to an isolated nucleic acids of SEQ ID NO: X or encoding a peptide of SEQ ID NO: Y, wherein X and Y are values that correlates to those listed in Table 1 and correspond to one of the cDNA clone IDs, respectively as well as vectors host cells and methods of making a proteins.

For example, If Group 1 is elected, this correlates to Gene No. 1, ATCC Deposit No. PTA02332, SE ID NO: 2 and SEQ ID NO: Y

It is noted that the Groups would be numbering 7, if the X and Y sequences are limited to each row. The Groups number 49, if one can pick and choose a separate X and a separate Y from Table 1.

Applicant is invited to clarify the number of possibilities intended.

Groups 50-98, claims 11, 12 and 16, all in part, drawn to proteins comprising sequences encoded by SEQ ID NO: X and a peptide of SEQ ID NO: Y, wherein X and Y are values that correlates to those listed in Table 1 and correspond to one of the cDNA clone IDs, respectively.

Groups 99-147, claim 13, all in part, drawn to an antibody that binds a protein comprising sequences encoded by SEQ ID NO: X and a peptide of SEQ ID NO: Y, wherein X and Y are values that correlates to those listed in Table 1 and correspond to one of the cDNA clone IDs, respectively.

Groups 148-196, claim 17 , all in part, drawn to methods of preventing or treating a medical conditions with an isolated nucleic acids of SEQ ID NO: X or encoding a peptide of SEQ ID NO: Y, wherein X and Y are values that correlates to those listed in Table 1 and correspond to one of the cDNA clone IDs, respectively.

Groups 197-245, claim 18, all in part, drawn to methods of diagnosing a pathological condition via an isolated nucleic acids of SEQ ID NO: X or encoding a peptide of SEQ ID NO: Y, wherein X and Y are values that correlates to those listed in Table 1 and correspond to one of the cDNA clone IDs, respectively.

Groups 246-294, claim 19, all in part, drawn to methods of diagnosing a pathological condition via an antibody that binds a protein encoded by isolated nucleic acids of SEQ ID NO: X or encoding a peptide of SEQ ID NO: Y, wherein X and Y are values that correlates to those listed in Table 1 and correspond to one of the cDNA clone IDs, respectively

Groups 295-343, claims 20-21, all in part, drawn to methods of identifying a binding partner of a peptide encoded by isolated nucleic acids of SEQ ID NO: X or encoding a peptide of SEQ ID NO: Y, wherein X and Y are values that correlates to those listed in Table 1 and correspond to one of the cDNA clone IDs, respectively

Groups 344-392, claim 22, all in part, drawn to methods of preventing or treating a medical condition with a protein encoded by the nucleic acids of SEQ ID NO: X or encoding a peptide of SEQ ID NO: Y, wherein X and Y are values that correlates to those listed in Table 1 and correspond to one of the cDNA clone IDs, respectively.

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack Unity of Invention because they are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for more than one species to be searched, the appropriate additional search fees must be paid. The species are as follows:

The polynucleotides and polypeptides of each of the claims in Table 1 are unrelated, each to the other. The polynucleotides sequence encode structurally distinct polypeptides and do not share a special technical feature. Further the technical feature that links the DNA,proteins, antibody and methods is not a contribution over the prior art of Corixa Corporation (WO 00/36107), particularly SEQ ID NO: 391. Also, see the Search Report. Thus, the technical feature of the polynucleotide sequence is not special and the Groups are not so linked under PCT Rule 13.1. Additionally the claimed methods encompassed different ingredients, process steps and endpoints, which are not so coextensive and which do not share the same technical feature.

The polynucleotides and polypeptides of each of the clones in Table1 are unrelated, each to other. The polynucleotides sequences encode structurally distinct polypeptides and do not share a special technical feature. Furthermore, the technical feature that links the DNA, protein, antibody and methods of PTA-2332 is not a contribution over the prior art of Corixa Corporation (WO 00/36107), particularly SEQ ID NO: 391 set forth in the Search Report. Thus, the technical feature of the polynucleotide sequence is not special and the Groups are not so linked under PCT Rule 13.1. Additionaly, the claimed methods encompass different ingredients, process steps and endpoints which are not coextensive and which do not share the same technical feature.